AUGUST 1961
VOLUME 84
NUMBER 2

THE AMERICAN REVIEW OF RESPIRATORY DISEASES

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Medical Section of the National Tuberculosis Association

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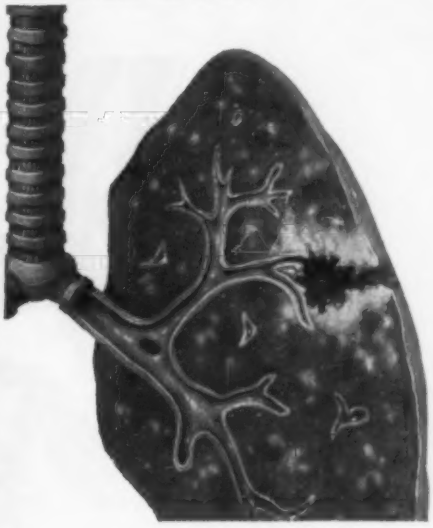

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1. Davey, W. N.: GP 19:107, No. 1, 1959.

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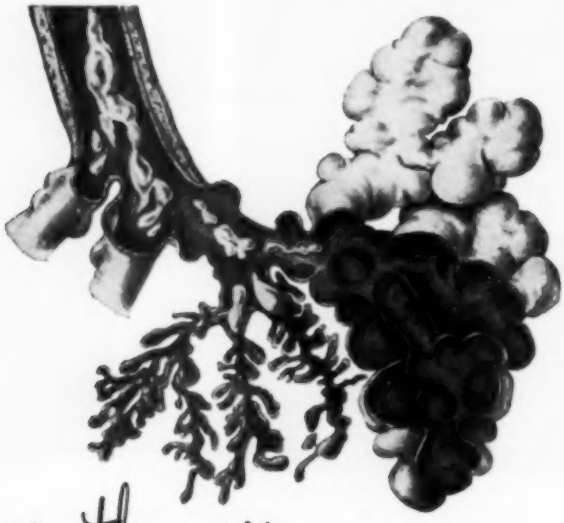

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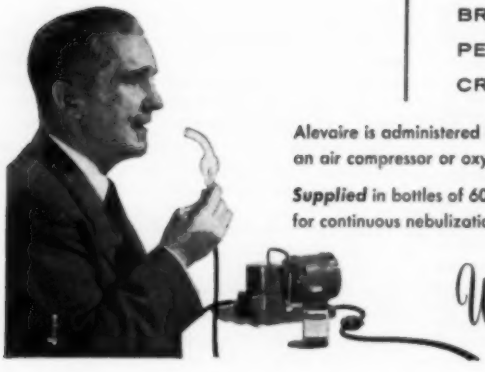

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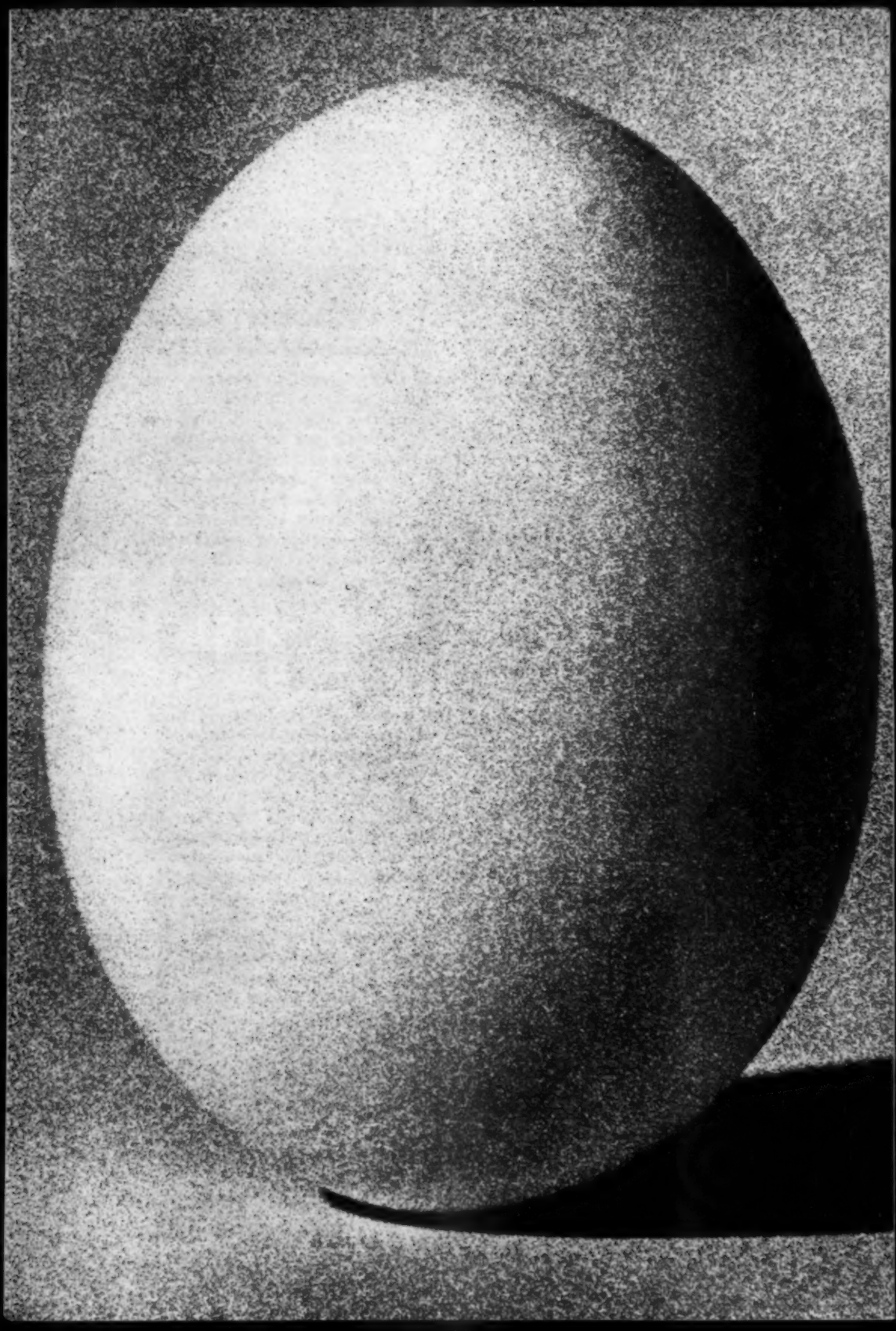

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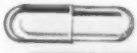

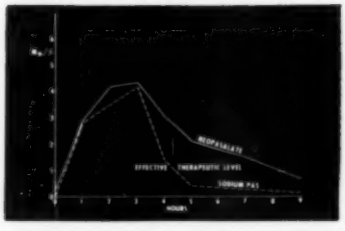

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In the June, 1961, issue of the REVIEW (volume 83), in the article entitled "Some Implications of the Addition of Tween® 80 to Dilutions of PPD Tuberculin with Respect to the Study of 'Specific' and 'Nonspecific' Tuberculin Sensitivity" by Gerard Wijsmuller, the term "PPD-Seibert (PPD-S)" was used. This should have been "*PPD-Standard (PPD-S)*."

In table 6 of the same article the subhead "Size of Reactions to 5 TU of RT 23 without Tween" should have read "*Size of Reactions to 5 TU of PPD-S without Tween*."

THE AMERICAN REVIEW
OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

VOLUME 84 *August* 1961 NUMBER 2

ILEOCECAL TUBERCULOSIS WITH PARTICULAR REFERENCE TO ISOLATION OF MYCOBACTERIUM TUBERCULOSIS[1, 2]

With a Note on Its Relation to Regional Ileitis (Crohn's Disease)

K. L. WIG,[3] N. L. CHITKARA, S. P. GUPTA, K. KISHORE, AND R. L. MANCHANDA

(Received for publication December 3, 1959)

INTRODUCTION

It is now more than a quarter of a century since Crohn and his colleagues (1) first described a condition which still bears his name, although nearly half a dozen other designations have been suggested by various workers. An enormous amount of literature has been accumulated on the subject during this period, yet the cause of the disease remains obscure (2). An editorial in the *Lancet* (3) sums up the present situation as, "perhaps after a quarter of a century, though we know the disease better, we understand it less."

However, despite the gap in our knowledge regarding the specific cause or cure of this disease, it is now widely believed in both England and the United States that a very large majority of cases of benign chronic granuloma of the ileocecal region (excluding those due to chronic appendicitis) are accounted for by Crohn's disease. The hyperplastic form of ileocecal tuberculosis which had been recognized as a clinical and pathologic entity for many years (4) seems to have been completely forgotten, and is now believed by some workers (5, 6) to be nonexistent. A leading textbook of medicine (7) states, "what has been described in the past as hyperplastic tuberculosis of caecum is probably a form of ileitis." A study of the *Cumulative Index* reveals that, while the number of publications on Crohn's disease has been steadily increasing over the last two decades, the reports on hyperplastic ileocecal tuberculosis are becoming fewer, which may reflect the infrequency with which the condition is being diagnosed. The present writers' experience in the northern part of India, however, is quite to the contrary (8, 9). A separate series of fifty hemicolectomies in patients with the hypertrophic type of ileocecal tuberculosis was reported by Anand (10) from this institution. In the present paper, the writers' 42 previously reported cases are reviewed and the series is extended by the addition of 25 new cases seen during the period 1955 to 1957. An additional feature is that the mycobacteria isolated from the intestinal wall and from the mesenteric or other lymph nodes have been classified.

MATERIALS AND METHODS

A total of 89 cases were studied. In 67, biopsy material of one form or another, such as mesenteric lymph nodes, portions of gut, or extra-abdominal lymph nodes, was available for histopathologic and bacteriologic studies. In the remaining patients, biopsy material was not available, but the clinical and therapeutic response of these patients very much resembled those of the other group. For the purpose of the present report, only 67 cases have been analyzed. These cases were collected over a period of four years (1953–1957) and represent only those patients who were admitted to the wards of the professor of medicine during this period. These figures do not represent the true

[1] From the departments of Medicine, Pathology, Bacteriology, and Clinical Surgery, Medical College, Amritsar, India.

[2] The first two years of this study were supported by grants from Punjab University, Chandigarh, and the last two years by the Indian Council of Medical Research, New Delhi, India.

[3] Present address: Department of Medicine, All-India Institute of Medical Sciences, New Delhi, India.

TABLE 1
AGES OF 67 PATIENTS WITH INTESTINAL TUBERCULOSIS

Age	Number of Patients
years	
Younger than 15	5
15 to 24	33
25 to 34	19
35 and older	10
	67

TABLE 2
SIGNS AND SYMPTOMS IN 67 PATIENTS WITH INTESTINAL TUBERCULOSIS

	Number of Patients
Pain in abdomen	57
Fever, usually low-grade	22
Diarrhea	7
Amenorrhea	16
Cough	12
Distended coils of intestines and/or visible peristalsis	12

incidence of the disease, as some patients could not be admitted due to great pressure on the available bed space in the hospital and because a number of patients were admitted to other units of this hospital.

The following investigations were carried out in each case:

Routine examination of the blood, urine, and stool.

Roentgenographic examination of the chest and the gastrointestinal tract.

Culture of sputum and/or gastric lavage for tubercle bacilli.

Bacteriologic and histopathologic examination of the mesenteric lymph nodes and/or resected loops of the small and large intestines or the extra-abdominal lymph nodes.

All of the tubercle bacilli that were isolated were classified.

OBSERVATIONS

Age and sex factors: The maximal incidence of the disease was in the age group of fifteen to twenty-four years (as may be seen in table 1), followed by the patients twenty-five to thirty-four years old. There were very few patients younger than fifteen years. The youngest patient in this series was 13 years old, and the eldest, 50 years. Of these 67 patients, 50 were women and only 17 were men. This high preponderance in women is all the more striking in view of the fact that the bed capacity in the female ward is comparatively less than that in the male ward.

History of contact and home environment: A definite history of contact with a known case of tuberculosis either in the same family or close neighborhood was available in only 16 patients in this series. A history of casual contact with doubtful cases was not taken into consideration. A history of having consumed unboiled milk either occasionally or repeatedly was available in 15 patients. Judged from their monthly income and the number of dependents in their families, the social status of 40 patients was poor, it was average for 26 patients, and only one patient belonged to the upper socioeconomic level. The housing conditions were poor for 34 patients and average for 33. Thirty-one patients lived in village surroundings, and 36 in urban areas.

Signs and Symptoms

The important signs and symptoms evident in the 67 patients are presented in table 2. The most common symptom was a mild pain in the abdomen, which was present in 57 patients. In nearly all of these patients a dull ache was present more or less constantly, with superimposed attacks of acute exacerbation accompanied by meteorism, distention of the abdomen, constipation and, occasionally, vomiting. Such attacks recurred at irregular intervals and usually lasted for a few hours or a day or two; they were relieved by the passage of flatus or by simple enemas, but they sometimes necessitated injections of atropine.

The duration of the complaints also varied widely, the shortest being twelve days and the longest twenty years. In 11 patients the symptoms had been present for less than six months; in 9 patients, from six months to one year; in 17 patients, from one to two years; in 22 patients, from two to five years; and in 8 patients, the symptoms had lasted more than five years.

A definite mass was palpable in the right iliac fossa in 49 patients. The mass consisted chiefly of thickened cecum; it varied in size from a walnut to an egg or larger; it was usually firm, but in some patients the mass was slightly tender upon deep pressure. The mass was usually fixed to the posterior abdominal wall or was only slightly movable within the abdomen. In another 7 patients, multiple masses which ap-

peared to be enlarged mesenteric nodes were present in the abdomen. The extra-abdominal lymph nodes were enlarged and palpable in 13 patients.

Clinical evidence of intestinal obstruction in the form of distended coils of intestine and/or visible peristalsis was present in 12 patients. Four patients had ascites. In one the ascitic fluid yielded tubercle bacilli on culture; the other 3 patients had enlarged extra-abdominal lymph nodes, and their biopsy specimens revealed histopathology typical of tuberculosis.

Laboratory Investigations

Routine blood tests (total and differential leukocyte count, hemoglobin, and erythrocyte determinations) and urine and stool examinations were carried out in each patient. Except for a moderate degree of anemia that was invariably present and cysts of giardia intestinalis in 2 patients, no other abnormality was detected.

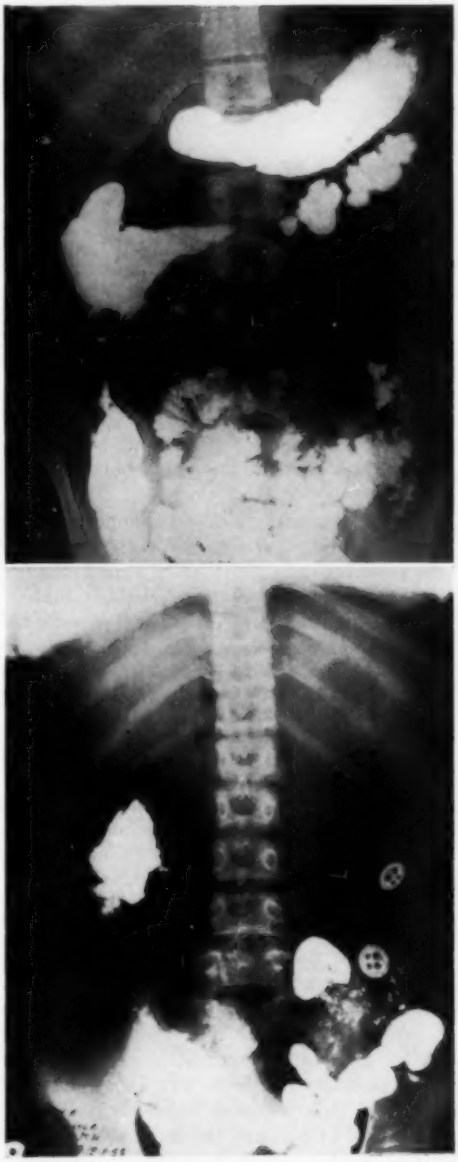
All of the patients were tuberculin reactors (Mantoux). The erythrocyte sedimentation rate was raised (more than 15 mm. by the Westergren method) in 48 patients, and was normal in the others.

Examination of sputum and/or gastric lavage for tubercle bacilli was done repeatedly in every patient, and a positive result was found in only one patient upon culture of gastric lavage.

A postero-anterior roentgenogram of the chest was taken in every case and, when indicated, a lateral view was also obtained. In 37 patients the roentgenographic examination of the chest was completely normal. In the remaining patients the abnormalities observed were as follows: active lung lesions in 4 patients, old healed lung lesions in 14, thickened pleura in 2 patients, and enlarged mediastinal lymph nodes in 10.

Biopsy material removed from portions of the gut and mesenteric nodes or the extra-abdominal lymph nodes of the 37 patients who had no roentgenographic evidence of lung lesions yielded cultures positive for tubercle bacilli in 14 of these patients.

The gastrointestinal tracts were examined by barium meal in 60 patients and by barium enema when considered necessary. A persistent filling defect in the region of the cecum with or without involvement of the terminal ileum and part of the ascending colon was observed in 42 patients (figures 1 and 2). Twelve patients showed evidence of small gut obstruction in the form of markedly dilated coils of the small intestines, usually jejunum. In one patient no definite filling defect was seen, but there was a



FIGS. 1 and 2. Barium study of gastrointestinal tract showing filling defect in the region of cecum and part of the ascending colon.

TABLE 3

TYPE AND EXTENT OF DISEASE REVEALED BY ABDOMINAL SURGERY IN 67 PATIENTS WITH INTESTINAL TUBERCULOSIS

	Cases
Thickening of cecum and adjoining portion of ascending colon/terminal ileum	23
Thickened cecum alone	6
Small bowel strictures:	
With ileocecal involvement	11
Without ileocecal involvement	13
Enlarged mesenteric lymph nodes alone	3
Total	56

marked delay in the passage of the barium meal, which reached the cecum only after ten hours.

Of the remaining 5 patients who did not show any abnormality on roentgenographic study of the gastrointestinal tract, there were 3 who had stricture of the small bowel without involvement of the ileocecum. The other 2 patients had palpable masses in the cecal area which on operation were found to be simply matted mesenteric nodes. The ileocecum was normal in these 2 patients.

Operative Findings

Exploration of the abdomen was done in 56 of the 67 patients (table 3). The most common finding was thickening of the cecum with involvement of the adjoining portion of the ascending colon and/or terminal ileum (23 cases). In the majority of these patients, the cecum was fixed to the posterior abdominal wall and surrounded by varying amounts of mesenteric fat. Some degree of dilatation of the terminal ileum was invariably present. The cecum alone was affected in 6 other patients, while isolated involvement of the ileum was never observed. Single or multiple small bowel strictures were present in 24 patients, and in 11 of these there was associated pathology in the ileocecal region. The mesenteric lymph nodes were enlarged to a varying degree in nearly all of these patients, and in some they were frankly caseating.

In 8 patients there were abnormalities beyond the area of the main pathology in the intestines in the form of multiple scattered miliary tubercles over the peritoneum, the surface of the liver and spleen, and/or the subserous coat of the small intestines.

In 3 patients the only finding was enlarged mesenteric lymph nodes with some degree of localized peritonitis.

A short-circuiting operation of one form or the other which bypassed the site of the main pathology responsible for the mechanical obstruction was possible in 47 patients. Of the remaining 9 patients, 3 had mesenteric adenitis alone. In the other patients, a bypass could not be provided either because the disease was so extensive that a sufficient portion of healthy small intestines proximal to the diseased area was not available for anastomisis (5 cases), or because the condition of the patient did not permit such an operation (one case).

In 17 patients a "second look" at the abdomen was possible when resection of the involved portion of the intestines was performed after intervals varying from three to ten months. All of these patients had received fairly intensive antimicrobial therapy (streptomycin and isoniazid-PAS) during this period. Compared to the findings on first exploration, a significant change for the better, in the form of greater localization of the pathology to the main diseased site and a reduction in the size and number of the mesenteric nodes, was observed in nearly all of the patients. This was especially evident in 2 patients in whom at the time of the first operation a spread of disease outside the intestine was present. The miliary tubercles on the surface of the peritoneum, liver, and spleen had disappeared. In only one patient had the appearance remained unchanged. Resection of the intestines could not be carried out in this patient as his condition suddenly took a serious turn during the operation. In the remaining 16 patients, hemicolectomies were done, and portions of the gut consisting of the cecum, ascending colon, part of the transverse colon, and varying lengths of the terminal ileum were removed. The cecum was found to be firm and contracted to various degrees, marked thickening of the cecal wall resulting in great narrowing of the lumen in all of the patients. In one patient the wall of the cecum was 3 cm. thick, and its lumen barely permitted the passage of a probe. The ileocecal junction was diseased and narrowed in all patients, sometimes to an extreme degree which did not permit the passage of the little finger (figure 3). The normal rugose pattern of the

mucosa of the cecum was lost, and in 4 patients ulceration was seen on the mucosal surface.

Histopathologic Study

In all of the patients diagnosed clinically as having abdominal tuberculosis, an attempt was made to examine histopathologically a mesenteric lymph node, and/or a resected piece of the small or large bowel, or an extra-abdominal lymph node from the neck or the axilla.

In the total series of 67 cases, 71 mesenteric lymph nodes, 18 resected pieces of gut, and 10 extra-abdominal lymph nodes were studied. The tissues were embedded in paraffin and sections were routinely stained with hematoxylin and eosin. During the first two years of the study, reticulum staining was also employed in all of the patients, but later this was done only selectively. During the early stages of the study, the sections were also stained by the Ziehl-Neelsen method for acid-fast bacilli. As virtually all sections were negative for acid-fast bacilli, this was later abandoned.

Lymph nodes: Histopathologic criteria for the diagnosis of tuberculosis were based on definite areas of caseation necrosis, epithelioid cell reaction, and giant cells of the foreign body or Langhan's type. In some patients the caseation necrosis was very widespread, occupying practically all of a lymph node except for a small rim at the periphery. At the other extreme, in some lymph nodes the necrotic area was minimal, occupying only a small area in the center of the follicles, the lymph nodes as a whole showing many false follicles. Most of the nodes covered a wide range between these two extremes. Epithelioid and giant cells could always be demonstrated in such cases. Some lymph nodes showed fibrosis and hyalinization only.

The mesenteric lymph nodes were examined in 55 patients at the time of the first operation. In 38, the histopathologic diagnosis of tuberculosis was made on the basis of the criteria set forth above. However, in 7 of the other 17 patients, the lymph nodes showed only reticular cell hyperplasia and false follicle formation. In another 8 patients, the specimens gave some suspicion of caseation necrosis, while in 2 patients there was marked hyalinization alone.

In 16 patients a second mesenteric lymph node was available for study after a period of four to six months. In 7 of these, caseation necrosis was either absent or was less marked and accompanied by more fibrosis and hyalinization. In 10 patients in whom mesenteric lymph nodes were not available, lymph nodes from either the neck or the axilla were examined, and all showed histopathology typical of tuberculosis.

FIG. 3. Figure showing thickening of wall of cecum with marked narrowing of its lumen.

Intestines: Resected loops of the large or small bowel were examined in 18 patients—hemicolectomy specimens in 16 and portions of the small bowel (with strictures) in 2 patients. In all of these specimens there was a general thickening of the intestinal wall in the diseased area. All of the layers showed diffuse as well as localized infiltration with round and plasma cells. In 2 patients eosinophilic infiltration was quite prominent. In 4 patients, in addition to the above changes there were areas of follicle formation with epithelioid cells and giant cells surrounded by a few strands of fibrous tissue (figures 4–6).

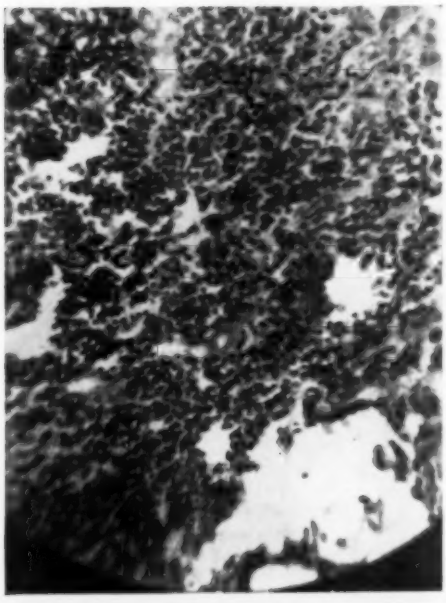
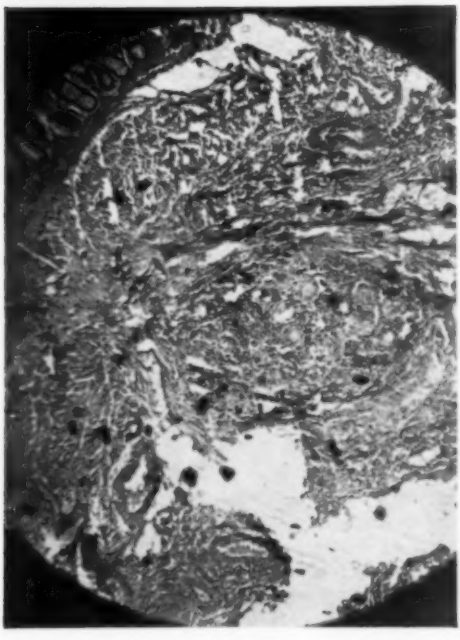
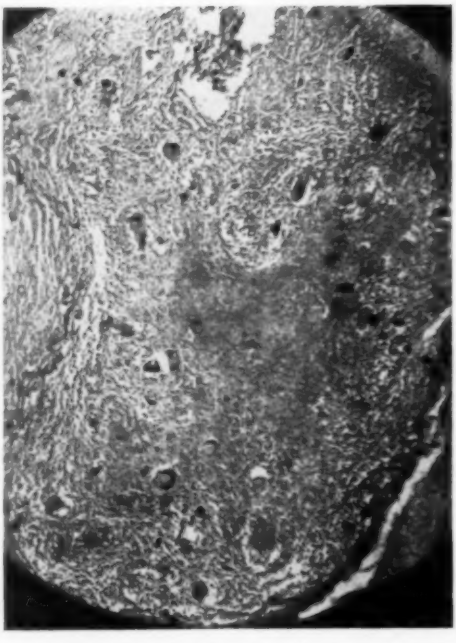


FIG. 4 (Upper). Section from wall of intestine showing diffuse round cell infiltration. (× 100)

FIG. 5 (Lower left). Section from wall of intestine showing follicle formation with giant cells and epithelioid cells. (× 100)

FIG. 6 (Lower right). Section from wall of intestine showing follicle formation with giant cells, epithelioid cells, and caseation necrosis in the center of the follicle. (× 100)





Bacteriology

In all 67 patients, the sputum and/or gastric lavage was routinely cultured for tubercle bacilli. In only one patient were tubercle bacilli isolated on culture of gastric lavage. However, bacteriologic examination for tubercle bacilli was made of the mesenteric lymph nodes and the walls of the small or large intestine. In cases

when the patient did not agree to an ileocolostomy or it was not considered desirable, an extra-abdominal lymph node from the axillary or neck region was cultured for tubercle bacilli when available.

The details of technique are discussed elsewhere (11). It may be mentioned, however, that Löwenstein-Jensen medium with and without glycerol was employed as a routine. In some cases the material was investigated by both culture and guinea pig inoculation. The mesenteric lymph nodes were employed in 55 cases, the intestinal wall alone or with the mesenteric lymph nodes in 18 cases, the ascitic fluid in 4 cases, the cervical or axillary lymph nodes in 10 cases, and the menstrual fluid in one case.

Twenty-six of these specimens yielded tubercle bacilli on culture. A fair amount of growth was obtained in all patients except 3 in whom the growth was very scanty and was lost on further subculture. A lung lesion in one form or another was detected roentgenographically in only 12 of these patients. In the others, the chest films were completely normal.

The tissue specimens that yielded tubercle bacilli were as follows: the mesenteric lymph nodes in 14 cases, the resected wall of the intestine and the mesenteric nodes in 2, the intestinal wall alone in 4, the cervical and axillary lymph nodes in 4, the ascitic fluid in one, and the menstrual blood in one.

This listing also includes 4 cases in which isolation of *M. tuberculosis* was obtained only by guinea pig inoculation. All of the cultures gave pigmented colonies. Some were lightly pigmented, while others gave marked pigmentation. Some of the cultures lost the pigmentation on prolonged incubation or during storage. Colonies were either discrete or confluent, and dry; they were occasionally moist, depending upon whether the growth was abundant or scant. The growth was obtained on Löwenstein-Jensen medium containing glycerol in a concentration of 1:10.75 per 100 ml. Although cultural characteristics such as the growth medium, the type of colony pigmentation, et cetera, were taken into consideration, final decisions on classification were reached only after animal inoculation.

One guinea pig and one rabbit were used at first for every strain, and later, two guinea pigs and one rabbit. The culture was weighed, suspended in sterilized normal saline, and inoculated intraperitoneally (and in some cases intramuscularly as well) into the rabbits, which averaged 1,000 to 1,200 gm. in weight, and the guinea pigs, which averaged 300 gm. in weight. Postmortem examination was performed after the death of each animal, or upon killing the animal if it did not die naturally after a lapse of at least twenty-four weeks. The guinea pigs inoculated intraperitoneally died after a period of one to 111 days (average, 29 days), and those inoculated intramuscularly died after 5 to 138 days (average, 53.5 days). The rabbits died after a period varying between 33 and 301 days, and averaging 199.3 days.

The viscera of all of the above-mentioned animals were carefully examined for any macroscopic evidence of tuberculosis, and portions of the spleen, liver, lungs, kidneys, parietal peritoneum, omentum, or intestinal walls were removed when they were suspected of containing lesions. These specimens were mashed and emulsified, and smeared and cultured for tubercle bacilli. Separate portions of these viscera were also prepared for histopathologic studies. The earliest histopathologic evidence of tuberculosis was obtained in a guinea pig which died 11 days after intraperitoneal inoculation of culture. The corresponding earliest period in the group of guinea pigs injected intramuscularly was 15 days. The following results were obtained: in 11 cases the guinea pigs developed tuberculous lesions, but the rabbits did not; in 4 cases tuberculous lesions were seen in both the rabbits and the guinea pigs; in 8 cases the results were inconclusive, and 3 strains were lost on subculture.

The four strains which had caused lesions in both the rabbits and the guinea pigs were investigated further. Various experiments were performed in which different doses of the organisms were given by different routes, i.e., subcutaneously, intramuscularly, intraperitoneally, and intravenously. A set of 3 animals was used for each dose and for each route. Additional similar experiments were performed with known virulent bovine and human strains, H37Rv, obtained from V.R.I. Izat Nagar, and C.R.I., Kasauli, respectively. The neutral red binding capacity and the amount of nicotinic acid synthesized by each strain as compared with known human and bovine strains were investigated. All of these investigations were done over a period of two years to find out if, by chance, any were bovine strains. After careful evalua-

tion of the results, it was decided that these four strains were human strains. The final conclusion, therefore, was that all of the strains of tubercle bacilli isolated and studied were human strains.

Discussion

The 67 cases analyzed above comprised a heterogeneous group of various forms of abdominal tuberculosis in which the most predominant type was hyperplastic ileocecal tuberculosis (49 cases). Each of the patients in the latter group had a palpable mass in the right iliac fossa and an identical clinical pattern with only minor variations in the severity of different symptoms. A study of the available biopsy material revealed: typical histopathologic changes of tuberculosis (*vide supra*), together with positive bacteriologic proof in 15 cases; histopathologic changes of tuberculosis without bacteriologic confirmation in 16 cases; and in 5 cases tubercle bacilli were isolated but histopathologic examinations showed only nonspecific inflammatory changes. In all of these 36 cases, therefore, the tuberculous etiology of the condition was definitely established. The absence of tubercle bacilli on cultures or guinea pig inoculation tests in 16 patients with histopathologic changes of tuberculosis in the mesenteric nodes or portions of the intestine does not in any way raise doubt as to the etiologic aspect of these cases. For, as is well known, such a correlation may not be forthcoming in every case.

The last subgroup of 5 cases is especially interesting and requires some comment. Under the microscope there were only nonspecific changes such as epithelioid cells, a few lymphocytes, and occasional giant cells with varying degrees of hyalinization. Caseation necrosis was strikingly absent, and yet tubercle bacilli were isolated in these cases. This suggests that, contrary to the usual accepted criteria for the histopathologic diagnosis of tuberculosis (especially of the lymph nodes and intestines) caseation necrosis may not always be present (12), and *that its absence alone should not be taken to exclude the possibility of an ileocecal granuloma's being tuberculous in nature* (4).

This was reaffirmed in another patient (case 12-B.D), in whom at the time of first operation the mesenteric lymph nodes yielded a negative culture but revealed classical histopathologic changes with a gross degree of caseation necrosis. Three months later, when hemicolectomy was performed, the mesenteric node and the portion of intestine removed showed only nonspecific inflammatory changes histologically, but yielded tubercle bacilli on culture. It is thus apparent that either caseation necrosis or the isolation of tubercle bacilli may be absent in an otherwise definite case of tuberculosis. Is it then not conceivable that in certain patients both of these criteria may be lacking and yet they may be tuberculous?

There were 13 cases in which neither criterium could be met in the study being reported. Clinically, roentgenographically, and on laporotomy they greatly resembled the other cases. An important question arises whether it is justified to label them as tuberculous, or might they be examples of nonspecific granuloma of the ileocecal region, probably Crohn's disease. Clinically and pathologically, the two conditions have much in common (4), although on this point also there is a wide difference of opinion (1, 13). Absence of caseation necrosis and failure to isolate tubercle bacilli have been the chief or perhaps the sole criteria for diagnosing these cases as examples of Crohn's disease. Unfortunately, tubercle bacilli can never be isolated from every tuberculous lesion, whatever the disease site. As for caseation necrosis, it has been established previously (8), in favorable cases at least, that the histopathologic appearance may change considerably with the progress of the disease, especially under specific antituberculous treatment. It is of some significance to note that, in the majority of these 13 unidentifiable cases, the symptoms were of several years' duration, and almost all of the patients presented with features of chronic and recurrent intestinal obstruction. It is possible that due to longstanding disease an active tuberculous pathology had burnt itself out, leaving in its wake only a thickened, scarred, and contracted segment of the intestine with enlarged nodes in which calcification was occasionally seen. Nontuberculous secondary infection of the damaged and deformed portion of the bowel, which is likely to occur, would further alter the histopathologic appearance. At this stage it is possible that, in some cases at any rate, the lesions may not show any evidence of tuberculous etiology, but only changes suggestive of what is known as Crohn's disease.

Retrospectively, a chain of histopathologic changes can be visualized in the biopsy speci-

mens from the cases reported here. While at one extreme there were the florid cases in which all of the tissue was virtually replaced by caseation necrosis, some cases showed only moderate or slight caseation necrosis, while in still others it was completely absent. The changes were occasionally present in both the affected bowel wall and the regional mesenteric nodes, but quite often they were confined to the latter. Tubercle bacilli were isolated from all cases, irrespective of the presence or absence of caseation necrosis.

It is possible that with the passage of time less caseation necrosis and more fibrotic reaction may be seen in the histopathology of tuberculous lesions. Changes of this sort are not peculiar to tuberculosis and are often seen in many other diseases.

What may be of importance in the final production of histopathologic changes is the relation between the virulence of the tubercle bacilli and the immunity reaction of the host. As this reaction is likely to vary greatly in different countries, and from patient to patient in the same country, a wide range of histopathologic appearances, from frank caseation to its complete absence, may be seen in tuberculous lesions.

The writers are strongly of the view that hyperplastic ileocecal tuberculosis is a far more common condition (at least in India) than is currently believed, and that it probably accounts for a fairly large number of cases of chronic ileocecal granuloma of Crohn's type.

Summary

Clinical, histopathologic, and bacteriologic data of 67 cases of abdominal tuberculosis are presented, 49 of which were hyperplastic ileocecal tuberculosis. The latter group of cases is discussed in detail. It is argued that a culture positive for *M. tuberculosis*, or a guinea pig inoculation, and/or frank caseation necrosis, which have usually been regarded as necessary for a diagnosis of tuberculous lesions, may not always be present; their absence alone does not negate the diagnosis of ileocecal tuberculosis and suggest that of Crohn's disease. It should be realized that a hyperplastic form of ileocecal tuberculosis is not so uncommon as it has seemed to be, and that this form probably accounts (at any rate, in India) for a large number of cases of chronic ileocecal granuloma of Crohn's type. The tubercle bacilli isolated in all of the cases have been classified, and all were found to be human strains.

Sumario

Tuberculosis Ileocecal con Referencia Particular al Aislamiento del Mycobacterium Tuberculosis. *Con una Nota sobre su Relación con la Ileítis Regional (Enfermedad de Crohn)*

Se presentan datos clínicos histopatológicos y bacteriológicos de 67 casos de tuberculosis abdominal, 49 de los cuales eran de tuberculosis ileocecal hiperplásica. Se discute a fondo el último grupo de casos. Se arguye que tal vez no existan un cultivo positivo para *M. tuberculosis*, o una inoculación positiva en el cobayo y/o declarado esfacelamiento caseoso, que se han considerado habitualmente como necesarios para un diagnóstico de lesiones tuberculosas; su carencia por sí sola no vicia el diagnóstico de tuberculosis ileocecal y sugiere el de enfermedad de Crohn. Debe comprenderse que una forma hiperplásica de tuberculosis ileocecal no es tan rara como parecía ser, y que a esta forma corresponde (a lo menos en la India) un gran número de casos de granuloma ileocecal crónico de la forma de Crohn. Al clasificar los bacilos tuberculosos aislados en todos los casos, todos resultaron ser cepas humanas.

Resume

Tuberculose iléocaecale avec mention spéciale se référant à l'isolation de Mycobactérium tuberulosis. *Avec une note sur son rapport avec l'iléite régionale (maladie de Crohn)*

Les auteurs présentent les données cliniques, histopathologiques et bactériologiques de 67 cas de tuberculose abdominale, 49 d'entr'eux furent une tuberculose iléocaecale hyperplastique. Le dernier groupe est discuté en détail. On discute le fait qu'une culture positive pour *M. tuberculosis* ou une inoculation au cobaye, et/ou une nécrose caséeuse franche, qui ont été habituellement considérées comme nécessaire pour porter le diagnostic de lésions tuberculeuses, peut ne pas être toujours présente; leur absence seule n'annulle pas le diagnostic de tuberculose iléocaecale et fait penser à celui de la maladie de Crohn. On devrait réaliser qu'une forme hyperplastique de tuberculose iléocaecale n'est pas si rare qu'elle semble être, et que cette forme explique probablement (aux Indes en tout cas) un grand nombre de cas de granulômes iléocaecaux chroniques du type Crohn. Les bacilles tuberculeux isolés dans tous les cas ont été classés, et on trouva qu'ils étaient tous des souches humaines.

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PULMONARY ADAPTATIONS TO ALTERED THYROID METABOLISM[1, 2]

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INTRODUCTION

Abundant evidence in the literature suggests an intimate association between thyroid function and a variety of pulmonary disorders. Therapeutic benefit from I^{131}-induced hypothyroidism has been observed in patients with chronic obstructive pulmonary emphysema (1–3). Patients on prolonged treatment with medication containing inorganic iodine occasionally develop myxedema (4–10). When the drug is discontinued, rebound hyperactivity of the thyroid gland occurs (4, 5, 10), and patients with severe pulmonary handicaps have been reported to develop acute pulmonary insufficiency during this period of increased function (10).

For many years physicians have noted that hyperthyroid patients seldom develop active tuberculosis, while clinical and experimental studies indicate that hypothyroidism increases susceptibility to tuberculosis (11–14). With the advent of chemotherapy in tuberculosis, consideration should be given to the importance of the fact that para-aminosalicylic acid and isoniazid, to a less extent, are antithyroid drugs and that patients may become hypothyroid after six months of treatment with these drugs (15, 16).

The possible consequences must also be considered of administration of drugs commonly used in respiratory diseases that also affect thyroid function. For example, epinephrine is said to increase the basal metabolic rate and I^{131} uptake (17) while acetazoleamide is reported to decrease I^{131} uptake (18).

Therefore, it seemed worth while to investigate pulmonary function in patients with abnormal thyroid function but normal ventilatory capacity and with no detectable pulmonary disease and, in addition, in anesthetized hyper- and hypothyroid dogs in order to eliminate psychic influences.

MATERIAL AND METHODS

Seven hyperthyroid and 5 hypothyroid patients were selected who had characteristic history and physical and laboratory findings of marked abnormality in thyroid function. None had evidence of pulmonary disease as elicited by history and physical or roentgenographic examination. All had vital capacity and maximal breathing capacity within normal limits (19) and expired greater than 90 per cent of the vital capacity in three seconds (20). None were in heart failure or receiving thyroid medication at the time of the study. Ventilation and blood gas exchange were analyzed as described by Riley (21, 22).

With the patient in the supine position and breathing room air, arterial blood was obtained anaerobically from an indwelling needle or catheter in a peripheral artery simultaneously with the collection of expired air. The arterial oxygen and carbon dioxide tensions were measured in duplicate by the Riley bubble equilibration technique (23), 4 mm. checks being required. Expired air was analyzed with the Scholander apparatus (24), duplicate determinations being required to check within 0.03 per cent. Oxygen consumption was calculated by the amount of oxygen inspired minus the amount expired. The mean alveolar oxygen tension was calculated according to the alveolar equation (25) and the alveolar-arterial (A-a) oxygen difference was determined. Per cent venous admixture was calculated by the formula (21):

$$\frac{\text{alveolar capillary per cent saturation} - \text{arterial per cent saturation}}{\text{alveolar capillary per cent saturation} - \text{mixed venous per cent saturation}}$$

The alveolar capillary per cent saturation was calculated from the alveolar oxygen tension (P_{O_2}) and the standard oxygen dissociation curve. Mixed venous per cent saturation was assumed to be 25 per cent of the arterial oxygen saturation.

All ventilation measurements are expressed at body temperature, prevailing barometric pressure, and saturated with water vapor (BTPS). Oxygen consumption and blood gas values are reported in terms of dry gas at standard temperature and pressure (STPD). Except when calculating the

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TABLE 1

SUMMARY OF METABOLIC DATA IN PATIENTS WITH ALTERED THYROID METABOLISM

Patients	Age	Sex	O_2 Uptake	Basal Metabolic Rate	Cholesterol	P.B.I.*	I^{131}	Type
			cc./min./M²		*mg./100 ml.*	*γ/100 ml.*	*% in 24 hours*	
Hyperthyroid patients								
MT	32	F	172	+42	141	6.7	73	Diffuse toxic goiter
OB	19	F	185	+46	116	11.5	51	Diffuse toxic goiter
MH	33	F	214	+75	—	—	50	Diffuse toxic goiter
SC	39	F	193	+60	104	>12.0	60	Diffuse toxic goiter
JA	65	M	235	+105	142	>12.0	58	Diffuse toxic goiter
VM	43	F	216	+80	141	>12.0	77	Diffuse toxic goiter
PP	30	F	216	+78	157	11.2	79	Diffuse toxic goiter
Mean...	37		204	+69	134	>10.8	64	
Hypothyroid patients								
RW	15	F	110	−50	528	<1.0	1	Primary
NM	55	F	90	−25	380	4.7	12	Post hypophysectomy
SC	54	F	112	−8	483	<1.0	5	Post thyroidectomy
FM	41	F	95	−23	200	<1.0	7	Primary
MC	59	F	99	−15	400	—	5	Post thyroidectomy
Mean...	45		101	−24	398	<1.9	6	

*Protein-bound iodine

cubic centimeters of oxygen consumed per liter ventilated, the former is taken at BTPS.

To further investigate the effect of altered thyroid metabolism on lung function and to eliminate the psychic factor, studies were done on 10 dogs. Five had received 4.5 mg. per kg. of body weight of desiccated thyroid daily for eight weeks prior to the study, and 5 had had surgical removal of the thyroid gland eight weeks previously. After the animals were anesthetized by intravenous injection of 20 mg. per kg. of body weight of sodium pentobarbital, a cuffed endotracheal tube was inserted and an indwelling catheter was placed in the femoral artery. Pulmonary function studies were essentially the same as in the patients except that, in addition, the alveolar-arterial oxygen difference was determined during inhalation of 12 per cent oxygen and 30 per cent oxygen to evaluate pulmonary diffusion and venous admixture (21).

Statistical analysis of the data was done, using the paired *t*-test. The null hypothesis was rejected at the 5 per cent level of significance.

RESULTS

Hyper- and hypothyroid patients: Clinical and metabolic data, summarized in table 1, indicated that all patients had well defined hyper- or hypothyroid disease.

Ventilatory results are tabulated in table 2. Total ventilation (normal 2.5–5.0 L. per min. per M^2) was 7.0 L. per min. per M^2 in the hyperthyroid group as compared with 3.4 L. per min. per M^2 in the hypothyroid group ($P < 0.001$), while alveolar ventilation (normal 1.5 to 3.5 L. per min. per M^2) was 5.7 L. per min. per M^2 as compared with 2.7 L. per min. per M^2 ($P < 0.001$). This difference was due to the greater respiratory rate of 25 per min. in the hyperthyroid patients in contrast to 14 per min. in the hypothyroid patients ($P < 0.01$). Tidal volume (normal, 500 cc.) and dead space per cent of tidal volume (normal, <30 per cent) were normal in both types of patients and not significantly different. Efficiency of ventilation as measured by the amount of oxygen removed for each liter ventilated indicated a slight, probably insignificant, reduction from the normal of 40 cc. in both groups. It was noted, however, that the hyperthyroid subjects were unable to increase the extraction of oxygen during exercise (normal, 48 cc.) while the hypothyroid ones were not so handicapped.

Information relative to blood gas exchange is recorded in table 3. No significant differences were observed in the two groups. Arterial carbon dioxide tension (normal, 40 mm. of mer-

cury) was in the low normal range. Although alveolar oxygen tension was adequate (normal, 104 mm. of mercury), arterial oxygen tension (normal, 95 mm. of mercury) was reduced to 86 mm. of mercury in the hyperthyroid and 82 mm. of mercury in the hypothyroid patients. This resulted in a small but consistent increase in the A-a oxygen difference to 21 and 24 mm. of mercury, respectively (normal 10 mm. of mercury), and per cent venous admixture to 8 per cent (normal, <7 per cent). Neither arterial carbon dioxide nor oxygen tensions were altered by exercise.

Hyper- and hypothyroid dogs: Results in the experimental animals, shown in table 4, revealed almost identical information; namely, greater total and alveolar ventilation ($P < 0.05$) due to the faster respiratory rate in the hyperthyroid than in the hypothyroid dogs, with normal blood gas exchange except for slight abnormality in oxygenation. Although mean alveolar oxygen tension (normal, 99 mm. of mercury) was 103 mm. of mercury in the hyperthyroid group and only 95 mm. of mercury in the hypothyroid group, this proved not to be statistically different. Mean arterial oxygen tension (normal, 89 mm. of mercury) was 84 mm. of mercury with increased metabolism and 83 mm. of mercury with decreased metabolism. The alveolar-arterial oxygen difference breathing atmospheric air (normal, 11 mm. of mercury) was 19 and 12 mm. of mercury in the hyper- and hypothyroid dogs, respectively. During inhalation of 12 per cent oxygen, the A-a oxygen difference (normal, 9 mm. of mercury) was 6 mm. of mercury in both groups, indicating normal pulmonary diffusion. Abnormal venous admixture was present as shown by A-a oxygen differences during inhalation of 30 per cent oxygen (normal, 37 mm. of mercury) of 59 mm. of mercury in the hyperthyroid dogs and 51 mm. of mercury in the hypothyroid dogs. Per cent venous admixture calculated within normal range, however. The normal values quoted are those established for dogs in this laboratory under the experimental conditions used in the present study (26).

In addition, it was observed that the appearance of the two groups of dogs was quite different. The hyperthyroid animals were hyperactive with silky coats while the hypothyroid animals, in contrast, were quite lethargic with dull coats.

TABLE 2

SUMMARY OF VENTILATION STUDIES IN PATIENTS WITH ALTERED THYROID METABOLISM

Patient	Respiration	Tidal Volume	Ventilation	Alveolar Ventilation	Dead Space Per Cent of Tidal Volume	cc. O_2/L. Ventilation	
						Rest	Exercise
		(cc.)	L./min./M^2	L./min./M^2			
Hyperthyroid patients							
MT	22	413	6.0	5.0	18	34	25
OB	18	646	6.8	5.4	21	33	34
MH	19	445	5.7	5.4	5	45	36
SC	27	346	7.8	5.8	25	30	—
JA	31	521	9.7	6.5	34	29	—
VM	28	464	7.3	5.5	24	35	—
PP	30	425	8.7	6.3	28	30	36
Mean	25	466	7.0	5.7	22	34 (33)*	34
Hypothyroid patients							
RW	20	229	3.9	2.8	5	34	43
NM	17	358	3.8	3.1	19	28	45
SC	11	528	3.3	2.7	22	41	41
FM	7	747	2.9	2.3	22	39	46
MC	13	370	3.3	2.4	27	36	46
Mean	14	448	3.4	2.7	19	36	44

* Mean of patients with exercise studies

TABLE 3

SUMMARY OF BLOOD GAS STUDIES IN PATIENTS WITH ALTERED THYROID METABOLISM

Patient	Arterial CO_2		Alveolar O_2	Arterial O_2		Alveolar-Arterial O_2 Difference	Per Cent Venous Admixture
	Rest	Exercise		Rest	Exercise		
	mm. Hg.		*mm. Hg.*	*mm. Hg.*			
Hyperthyroid patients							
MT	32	25	100	84	92	16	6
OB	33	31	114	94	92	20	6
MH	32	41	108	78	84	30	11
SC	37	—	107	86	—	21	7
JA	39	—	107	91	—	16	6
VM	32	—	107	93	—	14	5
PP	35	37	108	76	78	32	12
Mean	34 (33)*	34	107	86 (83)*	87	21	8
Hypothyroid patients							
RW	33	35	107	86	82	21	5
NM	28	26	115	85	83	30	9
SC	32	27	103	77	91	26	10
FM	37	40	108	88	86	20	6
MC	40	39	98	76	81	22	9
Mean	37	35	106	82	84	24	8

* Mean of patients with exercise studies

TABLE 4

SUMMARY OF PULMONARY FUNCTION STUDIES IN DOGS WITH ALTERED THYROID METABOLISM

Dog	O_2 Uptake	Respiration	Tidal Volume	Ventilation	Alveolar Ventilation	Arterial CO_2	Alveolar O_2	Arterial O_2	A-a O_2 Difference			Per Cent Venous Admixture
									At Air	12% O_2	30% O_2	
	cc./min./M²		*(cc.)*	*L./min./M²*	*L./min./M²*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*			
Hyperthyroid dogs												
1	167	38	156	11.2	7.4	36	110	87	23	11	76	7
2	167	21	182	6.9	4.2	50	102	87	15	0	34	5
3	165	22	154	7.3	5.2	45	98	82	16	10	63	7
4	181	24	148	8.5	4.7	49	92	79	13	9	58	6
5	138	22	102	7.5	5.1	36	111	84	27	0	63	9
Mean	162	25	156	8.3	5.5	43	103	84	19	6	59	7
Hypothyroid dogs												
1	89	13	156	3.0	2.0	40	92	81	11	3	47	5
2	119	9	207	3.3	2.4	37	90	85	5	6	79	2
3	94	22	170	7.6	3.9	41	100	84	16	—	50	6
4	110	26	134	5.6	3.9	43	95	84	11	15	38	2
5	102	20	118	5.2	3.9	39	97	82	15	7	42	6
Mean	103	18	157	4.9	3.2	40	95	83	12	6	51	4

Discussion

The validity of pulmonary function studies in patients with thyroid disease might well be questioned. The significance of the present data is increased, it is believed, by the fact that both hyper- and hypothyroid subjects were studied in the same manner, at approximately the same time, and with the same personnel, the results subsequently being compared in the two groups. The difficulty of excluding psychic factors was recognized. An effort to minimize them, however, was made by discussing and explaining the proposed tests to the patient prior to his being brought to the laboratory. Studies were carried out in an unhurried and relaxed atmosphere and, if behavior or results indicated undue anxiety, the studies were repeated at a later date. Even so, it was considered desirable to perform these same studies in anesthetized animals with altered thyroid metabolism, thus virtually eliminating psychic influences.

The data indicate that, when normal lungs, normal neuromuscular systems, and central nervous systems are present, the body is able to adapt itself to abnormal metabolic states produced by thyroid disease by adjusting ventilation so that, except for slight abnormality in oxygenation, satisfactory blood gas exchange takes place. It is pointed out, however, that the hyperthyroid patients were unable to increase the extraction of oxygen during exercise. The slight increase above the normal for the alveolar-arterial oxygen difference is apparently due to venous admixture rather than to abnormal diffusion. In the hyperthyroid group this finding may be analogous to the known effect of voluntary hyperventilation or exercise, in which the alveolar oxygen tension is increased without a proportionate rise in arterial oxygen tension. In the hyperthyroid group it is most likely due to decrease in ventilation-perfusion ratios, a relatively high number of alveoli being underventilated. In the absence of pulmonary disease, this is probably of no clinical importance. These results support data obtained in other studies. In this laboratory it was found that total and alveolar ventilation consistently decreased in patients with severe chronic obstructive pulmonary emphysema following treatment with I^{131} (3). Although this was accompanied by no change in ventilatory capacity (vital capacity, timed vital capacity, and maximal breathing capacity), as a rule alveolar and arterial oxygen tension increased and arterial carbon dioxide decreased. Excellent or good clinical results, presumably because of the decrease in metabolic demands and, in turn, with decrease in ventilatory or breathing requirements, were obtained in 9 of 23 patients (39 per cent) followed for two and one-half years.

The opposite situation, acute pulmonary insufficiency and death of a patient with increased thyroid function which occurred after withdrawal of iodide medication when myxedema developed, was reported by Burrows, Niden, and Barclay (10).

Pulmonary function studies by Wilson and Bedell (27) in sixteen patients with myxedema without clinical lung disease revealed normal lung volumes and an increase in total and alveolar ventilation following treatment. Oxyhemoglobin saturation was normal (oxygen tension was not determined), carbon dioxide tension was within normal limits, and no change was noted after the patients became euthyroid. Those writers did, however, find the carbon monoxide diffusing capacity to be 69 per cent of normal before treatment as compared with 94 per cent after treatment. It is possible that ventilatory differences were partially responsible for this observation (28). Diffusion was normal in the hypothyroid dogs studied. Although diffusing capacity was not done on the patients in the present study, no fall in arterial oxygen tension occurred following exercise as would be expected with an "alveolar-capillary block" type of defect.

Although it is beyond the scope of this paper to discuss the numerous clinical implications, it does seem clear that the patient with ventilatory pulmonary insufficiency would be unable to meet easily the increased ventilatory demands necessitated by increased metabolism. Further decrease in breathing reserve, increase in dyspnea, and accentuation of both ventilatory and respiratory pulmonary insufficiency would be predicted. On the other hand, decrease in metabolic requirements with resulting decrease in ventilation would tend to have the opposite effect. The possible adverse effect of the hypothyroid state in tuberculosis must be remem-

bered, however. In addition, when considering cardiopulmonary status, one must also keep in mind that the cardiac output is usually increased in thyrotoxicosis and decreased in myxedema.

Summary

Pulmonary function in 7 hyperthyroid and 5 hypothyroid patients without evidence of pulmonary disease and with normal ventilatory capacity indicates that the body adapts to abnormal thyroid metabolism by alteration in ventilation, essentially normal blood gas exchange being maintained. Both total ventilation and alveolar ventilation were significantly greater in the hyperthyroid group than in the hypothyroid group. These findings were confirmed in similar studies on anesthetized hyper- or hypothyroid dogs, thereby eliminating the psychic factor as the cause for the difference in the two groups.

Possible clinical implications are briefly mentioned. This study suggests that the patient with pulmonary disease should be protected as much as possible against any treatment or situation that will increase metabolic demands.

Sumario

Adaptaciones Pulmonares a un Metabolismo Tiroideo Alterado

La función pulmonar observada en 7 sujetos hipertiroideos y 5 hipotiroideos sin signos de enfermedad pulmonar y con capacidad ventiladora normal indica que el organismo se adapta a un metabolismo tiroideo anómalo alterando la ventilación y manteniendo un intercambio esencialmente normal de gases en la sangre. Tanto la ventilación total como la alveolar fueron decididamente mayores en el grupo hipertiroideo que en el hipotiroideo. Se confirmaron estos hallazgos en estudios similares realizados en perros hiper- o hipotiroideos anestesiados, eliminando así el factor psíquico como causa de la diferencia entre los dos grupos.

Se mencionan brevemente las posibles connotaciones clínicas. Sugiere este estudio que, al sujeto con afección pulmonar, debe protegérsele en todo lo posible contra todo tratamiento o situación que acreciente las demandas metabólicas.

Resume

Adaptations pulmonaires aux changements de métabolisme thyroïdien

La fonction pulmonaire chez 7 malades hyperthyroïdiens et 5 hypothyroïdiens, sans évidence de maladie pulmonaire et avec une capacité ventilatoire normale, indique que le corps s'adapte à un métabolisme thyroïdien anormal par un changement dans la ventilation, les échanges gazeux du sang étant maintenus essentiellement normaux. La ventilation totale et la ventilation alvéolaire furent toutes les deux notablement plus grandes dans le groupe hyperthyroïdien que dans le groupe hypothyroïdien. Ces données furent confirmées dans des études semblables sur des chiens hyper- ou hypothyroïdiens anesthésiés, éliminant par conséquent le facteur psychique comme cause de différence entre les deux groupes.

Les auteurs mentionnent brièvement les implications cliniques possibles. Cette étude fait penser que le malade avec une maladie pulmonaire devrait être protégé autant que possible contre n'importe quel traitement ou situation qui augmente les demandes métaboliques.

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THE SURGICAL MANAGEMENT OF LARGE PULMONARY BLEBS AND BULLAE[1, 2, 3]

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INTRODUCTION

Pulmonary blebs and bullae represent more or less localized expressions of underlying obstructive emphysematous disease. Although the pathogenesis of obstructive emphysema is incompletely understood, it is a degenerative parenchymal disease which seems to be initiated by chronic bronchitis and bronchiolitis resulting in partial obstruction of the smaller air passageways and distal entrapment of air. As described by Miller (1), a bleb is the result of subpleural alveolar rupture with dissection of air into the subpleural areolar tissue plane. Bullae result from the intraparenchymal rupture of attenuated alveoli into each other, thereby resulting in multiloculated cystic spaces traversed by trabeculae comprised of alveolar septal elements and communicating with many bronchioles. From the clinical standpoint, there seems to be no practical importance in differentiating between these processes.

On the other hand, it is of considerable importance to differentiate these cystic lesions associated with obstructive emphysema from other types of cystic pulmonary disease, namely congenital bronchogenic cyst, pulmonary sequestration, chronic cystic bronchiectasis, chronic lung abcess, pneumatocele formation following staphylococcal pneumonia, and the localized emphysematous cystic manifestations which may occur secondary to partial bronchial obstruction by foreign bodies or tumors. A discussion of the pathogenesis and differential diagnosis of these various cystic pulmonary diseases has been made in a very apt report by Belcher and Siddons (2).

Despite the appearance of a number of excellent reports on this topic during the past fifteen years, there remains considerable difference of opinion regarding the selection of cases for operation, the preferable operative approach and technique, and the degree and permanence of improvement which can be achieved. It is the purpose of this report to outline certain concepts of the surgical management of large pulmonary blebs and bullae formulated from an operative experience with 14 cases.

OBSERVATIONS

Clinical Manifestations

Obstructive emphysema associated with blebs and bullae is primarily a disease of males in the fifth and sixth decades of life. Among the 14 operative cases in the present study, there were 12 males and 2 females, and the ages ranged from twenty-two to sixty-two years.

The most common presenting complaint was that of a long-standing irritative cough accompanied by the insidious development of progressive shortness of breath on exertion. Along with this there might be vague deep-seated chest discomfort or frank pain which was related to increasing distention of emphysematous air sacs associated with parenchymal compression and, particularly, pleural stretching. In conjunction with these symptoms, especially among those patients with more advanced obstructive emphysema, there was general malaise, easy fatigue, and often weight loss and nutritional debility. In some patients, the abrupt onset of acute shortness of breath heralded the occurrence of a spontaneous pneumothorax secondary to rupture of a bleb or bulla. In the present report, however, cases of spontaneous pneumothorax resulting from emphysema with air cyst rupture and treated by closed thoracotomy drainage were not included unless they

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later came to definitive thoracotomy and excisional procedures for large blebs or bullae.

A number of patients, particularly from the lower income group, reported for treatment only when their symptoms had become so severe as to be totally incapacitating. One patient had been bedridden for two and one-half years because of extreme shortness of breath and associated debility. On the other hand, a 23-year-old male was essentially asymptomatic but had tremendous bullous involvement of the right middle lobe associated with compression atelectasis of the lower lobe. This disparity between the clinical and roentgenographic features, as will be discussed, relates to the severity of the associated diffuse obstructive pulmonary emphysema.

The roentgenographic findings in obstructive emphysema with bullous formations are easily confused with spontaneous pneumothorax. One patient in the series had been treated in error by closed thoracotomy. The frequently multiloculated rounded or oval areas of increased radiolucency crossed by trabeculae, along with evidences of adjacent compressed pulmonary parenchyma, are characteristic. It is important to avoid overpenetration, as bullous changes may be masked on "burned out" films.

Pulmonary Function Studies

A satisfactory physiologic classification of these abnormal air spaces does not exist. Baldwin and associates (3) attempted to separate their cases on the basis of freedom of communication with the bronchial tree and the presence or absence of obstructive emphysema in the remaining lung. It has been difficult to group patients according to their criteria and, indeed, the separation of their own patients does not appear completely clear.

Others have noted a broad spectrum from completely normal pulmonary function to the findings which are characteristic for diffuse nonbullous obstructive emphysema (4–6). Much of the confusion relating to the pathophysiology of abnormal air spaces is concerned with the criteria for surgical removal. With patients who are largely asymptomatic, the pulmonary physiologic studies would be expected to be and have been found to be normal (5, 6). It is not clear from the literature whether lesions of this type are progressive and, although surgery in these patients is usually uncomplicated, it has been difficult to evaluate any functional improvement.

At the other extreme are patients crippled with extensive and diffuse bullous changes replacing most of the functioning lung tissue and not significantly differing physiologically from nonbullous pulmonary emphysema. Between these two extremes are the majority of patients who have variable degrees of clinical and physiologic impairment. Although, in general, patients with evidence of advanced emphysema have been considered poor candidates, it is within this group of subjects that palliative surgery when feasible offers most. It has been reported by Fitzpatrick and co-workers (7) that there is often physiologic evidence of progression of the emphysema in the late postoperative period, but the addition of several years of comfortable life may well be worth the additional surgical risk.

Of the 14 patients comprising this report, some physiologic data were obtained on 8, with pre- and postoperative data on the 4 most disabled patients. The pre- and postoperative ventilation studies on these 4 patients are shown in table 1 and summarized in figure 1. The mean preoperative maximal breathing capacity was 34 per cent of predicted. Postoperatively this value increased to a mean of 63 per cent of predicted. The preoperative mean vital capacity of 45 per cent of predicted rose to 74 per cent postoperatively. It should be noted that all of these 4 patients showed evidence of considerable emphysema preoperatively, but all showed, in addition, evidence of severe lung compression as judged by markedly reduced vital capacities.

Selection of Cases for Operation

The criteria for resecting blebs and bullae, unlike those for most other thoracic pathologic entities, remain unsettled. Much of the difficulty relates to the fact that these cases cannot be categorized according to their pulmonary function. In addition, a sufficient number of adequate long-term postoperative follow-up studies is not yet available and it is, accordingly, impossible to delineate the degree and permanence of improvement to be expected. Laminagrams, bronchograms, and angiocardiograms may be useful in demonstrating the degree of parenchymal compression produced by blebs or bullae and are accordingly of help in evaluating the possible benefits to be derived from operative

TABLE 1

PRE- AND POSTOPERATIVE VENTILATION STUDIES ON FOUR MOST DISABLED PATIENTS

Patient	Age	Sex	Height	BSA	MBC	VC	1-Second VC	Residual Volume	Total Lung Capacity	Pulmonary Mixing Index	Arterial		
											O_2 Saturation	pH	P_{CO_2}
			cm.	*sq. met.*	*(% of predicted)*	*(% of predicted)*	*(% of total)*	*(% of predicted)*	*(% of predicted)*	*(% N_2)*	*per cent*		*mm. Hg*
J.A.	56	M			52	47							
6 months p̄ op*			179	1.95	80	68							
E.F.	52	M	163	1.79	31	61	41	197	124	10.07	93	7.38	43
2 years p̄ op					61	89	42	88	96	5.54			
M.H.	49	F	170	1.46	24	29	48	138	77	6.10	79	7.36	58
4 months p̄ op					68	61	28	168	102	4.28	98	7.36	43
A.R.	62	M	173	1.64	28	43	46						
2 months p̄ op					42	78	40	156	112	3.07	95	7.42	40

BSA = body surface area
MBC = maximal breathing capacity
VC = vital capacity
* p̄ op = Postoperatively

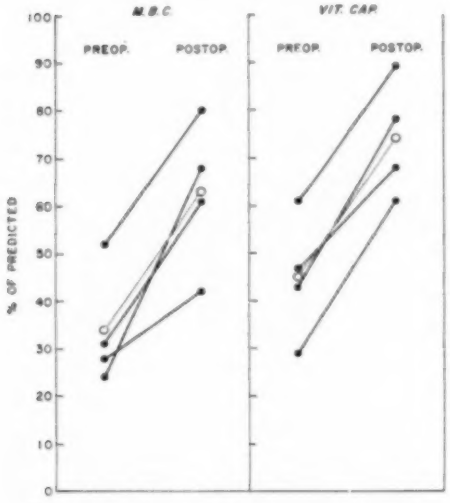

FIG. 1. Ventilatory performance in the 4 patients with pre- and postoperative studies. Each patient is represented by a closed circle. The mean of each study is indicated by an open circle.

intervention. Fluoroscopy, by providing a dynamic picture of the pulmonary pathology, allows a rough estimate of differential pulmonary function and is likewise helpful in preoperative assessment. Currently, the criteria of the present writers for operation can be summarized as follows (table 2):

1. *Any bleb or bulla occupying one-third or more of the hemithorax, whether or not it is productive of symptoms:* A space-occupying lesion of this size is productive of significant bronchopulmonary compression and, it is believed, will ultimately be associated with impaired drainage, infection, and permanent damage to the adjacent compressed lung tissue. Essentially, this conforms to the same criterion of bronchopulmonary compression generally employed for decortication operations.

2. *Blebs or bullae of large size associated with spontaneous pneumothorax:* A pleurodesis procedure is performed in addition to excision of the air cysts in the case of large blebs or bullae associated with spontaneous pneumothorax.

3. *Large unilateral or bilateral blebs and bullae associated with significant bronchopulmonary compression in patients with severe diffuse obstructive emphysema:* Admittedly the risk of surgery is high

TABLE 2

CRITERIA FOR RESECTING BLEBS AND BULLAE

1. Any bleb or bulla occupying ⅓ hemithorax, whether or not symptomatic
2. Blebs or bullae of large size associated with spontaneous pneumothorax
3. Large uni- or bilateral blebs or bullae associated with bronchopulmonary compression in patients with severe diffuse obstructive emphysema
4. Infection and hemorrhage (rare).

in the group of patients with significant bronchopulmonary compression, but the results are most rewarding. It is the writers' contention that, contrary to previous beliefs, diffuse alveolar insufficiency, even with accompanying cor pulmonale, is not an absolute contraindication to thoracotomy when significant bronchopulmonary compression by blebs and bullae can be demonstrated. Surgery, in this instance, is not curative of the underlying emphysematous disease but is of great palliative benefit, serving to rehabilitate a respiratory cripple.

In the present series, 7 patients, 3 of whom were studied extensively pre- and postoperatively by pulmonary function tests and gas analyses, belong in this category. All were gratifyingly rehabilitated following surgery.

4. *Infection and hemorrhage* associated with blebs and bullae are very infrequent indications for surgery.

Preoperative Preparation

In all of these patients, the postoperative course can be remarkably ameliorated by diligent preoperative preparation. The foremost consideration is the elimination of bronchitis and retained tracheobronchial secretions, and basic to this is the cessation of smoking for a period of at least two weeks prior to surgery. Every patient in the series had been a heavy cigarette smoker; in fact, except for a few patients with emphysema secondary to chronic bronchial asthma, obstructive emphysema has in the writers' experience been invariably associated with many years of cigarette smoking. Whether or not this is a cause-and-effect relationship cannot as yet be determined, but there seems to be little question that the chemical bronchitis resulting from tobacco smoke abets the development and progress of obstructive emphysema.

Adjuvant measures include intermittent positive pressure breathing treatments, expectorants, antimicrobials, and, in the very poor risk patients, steroid treatment. Bronchoscopy may be helpful and is mandatory in any case in which there is suspicion of a bronchial obstructing lesion. Elective tracheostomy allows the application of surgery to patients who have virtually no respiratory reserve. As is well known, tracheostomy reduces ventilatory dead space, provides ready access to the tracheobronchial tree for both catheter suctioning and the administration of oxygen, and permits application of internal respiratory assistance by means of a mechanical ventilator if necessary during the postoperative period.

Many of the patients were in very poor nutritional status, and some exhibited electrolyte derangement associated with chronic respiratory acidosis. All of these problems should be carefully evaluated and remedied insofar as possible before surgery.

Operative Technique

In each of the 14 patients included in this report, operative approach was by standard posterolateral thoracotomy, entering the pleural space via the fifth or sixth intercostal space. More recently, however, several patients suffering from recurrent spontaneous pneumothorax have been operated upon. It has been found that an anterior intercostal approach through the fourth interspace combined, if necessary, with transection of one, two, or three proximal costal cartilages, as recommended by Feraru and Morrow (8), provides very satisfactory exposure for excision of blebs and parietal pleurectomy. This incision, made with the patient in the supine position, interferes least with respiratory physiology during open thoracotomy. In addition, following the use of the anterior approach, less incisional discomfort and better postoperative ventilation have been observed than with the standard posterolateral incision which, of course, is carried through heavy musculature of the shoulder girdle. The major disadvantage of anterior thoracotomy is the somewhat limited accessibility to the pulmonary hilum when segmental resection or lobectomy are indicated. However, it is believed that the physiologic advantages outweigh this technical consideration.

Eight of the 14 operative cases underwent pulmonary resection, which included six lobectomies and two segmental resections. In all of these cases, the pulmonary parenchyma was destroyed by bleb and bullous formations which precluded the possibility of reconstituting the involved lobe by local excisional procedures (figures 2*A*, 2*B*, and 2*C*). In 4 of the 8 patients who underwent pulmonary resection, blebs and bullae were also excised from the remaining lobes and, in all but one of these patients, much of the remaining lung was noted to be emphysematous (figures 3*A* and 3*B*).

The remaining 6 patients were treated by local excision or "unroofing" and oversewing of the air cysts. In each case, satisfactory re-expansion of previously compressed pulmonary

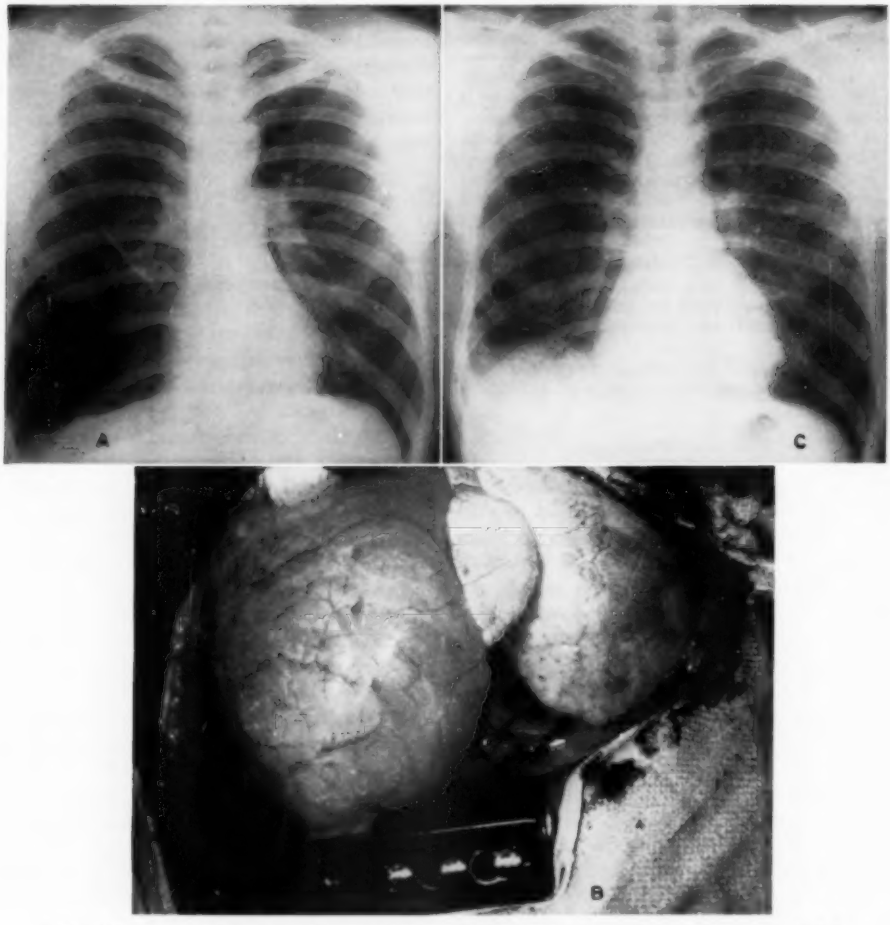

FIG. 2A. Large bullous formation, right lower lung field. *B*. The bullous mass is noted to arise from the medial segment of the right middle lobe. The lateral segment of the middle lobe perches on it like a cap and there is some compression atelectasis of the underlying lower lobe. *C*. Postoperative appearance following segmental resection of bullous lesion involving medial segment, middle lobe, and excision of small blebs from the superior segment of the lower lobe.

parenchyma was achieved, although it was apparent that these lungs uniformly were comprised of overdistended, firm, spongy emphysematous tissue.

In only 3 of the 14 patients were adhesions present between the visceral and parietal pleurae. These adhesions were invariably of fibrous, strandlike nature and were limited to the area of bleb and bullous formation which, in each of these cases, was located in the apical area. The absence of adhesions in the great majority of these cases was frequently noted, and prompted the adoption of a two-stage intracavitary drainage procedure by Head and Avery (9). Whereas this technique provided a great deal of stimulus to the surgical treatment of air cysts and may be applied successfully to the poor-risk patient with a discrete giant air cyst which is peripheral in location, the present writers have been deterred from applying it

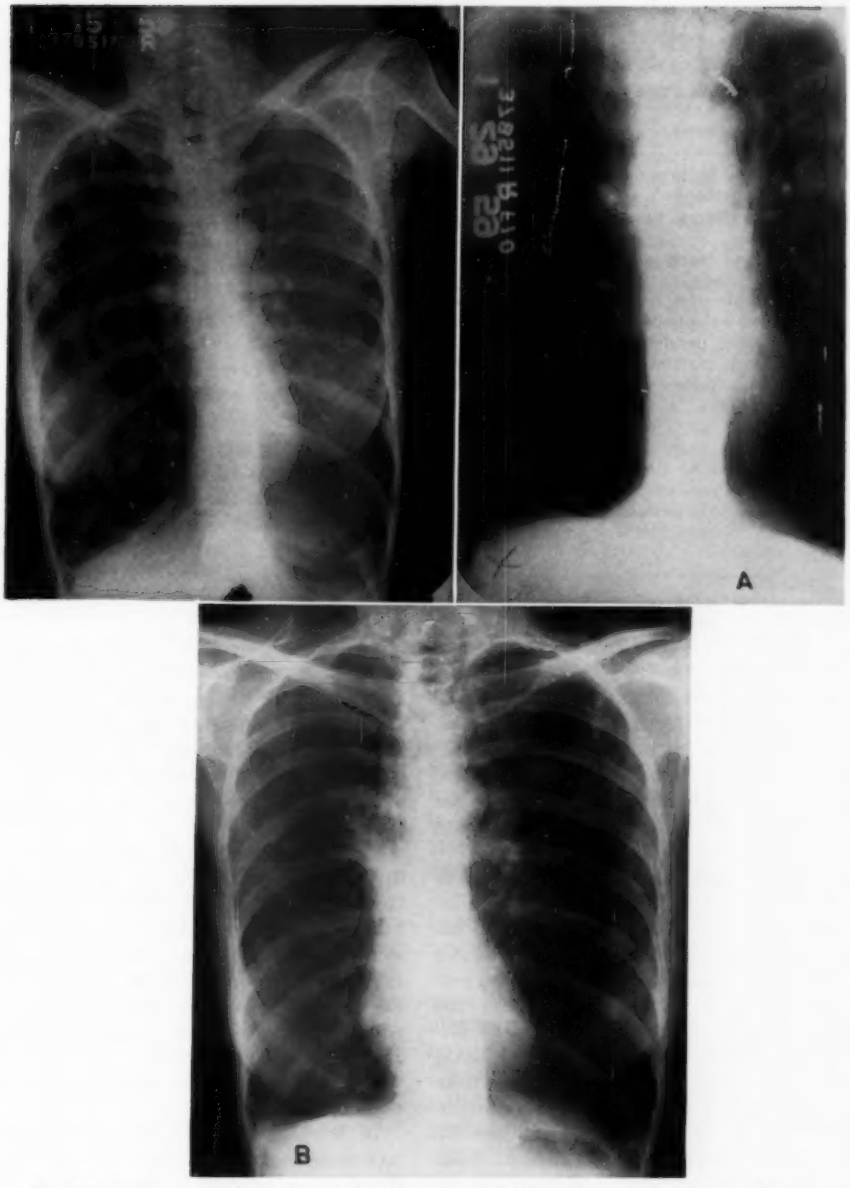

FIG. 3A. Preoperative chest film and laminagram revealing diffuse obstructive emphysema with virtual total replacement of the right lung by bullous formations and lesser bullous involvement of the left lower lung field. *B*. Appearance following right upper lobectomy and excision of blebs from the middle and upper lobes. Note dramatic reappearance of parenchymal markings on the right.

TABLE 3
POSTOPERATIVE COMPLICATIONS
(Three patients all had bilateral bullous emphysema.)

Patient	Complications	Therapy
M.H.	Retained secretions; enlargement of contralateral cysts	Bronchoscopy
F.H.	Retained secretions; atelectasis; contralateral cyst rupture; pneumothorax, persistent bronchopleural fistula, and loculated empyema	Bronchoscopy, tracheostomy, closed thoracotomy (contralateral), and later rib resection drainage
E.F.	Retained secretions; atelectasis; loculated apical empyema; enlargement of contralateral cysts	Tracheostomy (at time of surgery), open thoracotomy drainage

because of the two-week delay between the stages and the observation that most large emphysematous air cysts are loculated and may not be readily accessible to external drainage. In the present series of cases, for example, the air cysts were located primarily in the upper lobes in 9 cases and in the lower lobes in 5 cases. However, there were multiple smaller blebs and bullae arising from the upper, middle, and lower lobes in 6 cases.

In none of these patients was any type of pleurodesis procedure performed. Although no ultimate restriction of pulmonary function has been noted following these procedures, bleeding into the pleural space has been a problem, particularly following parietal pleurectomy, and there has been unwillingness to create any further surgical problems in these patients, many of whom are already very poor operative risks. Also, although it has not been observed to the present time, the development of additional air cysts requiring reoperation is a distinct possibility, the thought of which has prompted the handling of the pleural surfaces with utmost respect.

Maintenance of a clear tracheobronchial tree during surgery by brief but diligent suctioning is generally handled well, but the anesthetist must be cautioned to employ restraint in the application of positive pressure insufflation. This is particularly difficult when the patient is suffering from marked ventilatory insufficiency, but hyperinflation creates the hazard of enlarging or actually rupturing blebs or bullae, especially on the contralateral unseen side in instances of bilateral bullous disease. Dugan and Samson (10) reported one fatality in their series of 14 cases from this very cause. Gravenstein (11) has reported the occurrence of a nearly fatal pneumothorax and pneumomediastinum following the inadvertent application of high pressure to a cuffed intratracheal tube during anesthesia for a urologic procedure, and the present writers have recently seen the same phenomenon during orthopedic surgery.

Elective tracheostomy was performed at the time of thoracotomy in one of the present cases and was carried out five days later in another patient who continued to have difficulty due to retained secretions which could not be handled satisfactorily by diligent nasotracheal suctioning and repeated bronchoscopy.

Postoperative Complications

In virtually every case in which air cysts were unroofed and oversewn, there was a considerable air leak during the early postoperative period. However, with diligent attention to ensuring maximal expansion of the lung to fill the pleural space, all of these leaks ultimately sealed without the development of persistent bronchopleural fistulas.

In 3 cases there were complications (table 3). All of these patients were respiratory cripples due to severe bilateral blebs and bullae and had complications relating to retained bronchial secretions and to enlargement or rupture of air cysts on the unoperated side. In one of these the problem of retained secretions was readily corrected by a single bronchoscopic application. However, certain of the contralateral bullae were observed to increase slightly in size during this time.

In a second patient, repeated nasotracheal suctioning, bronchoscopy and, ultimately, tracheostomy were required to handle recurrent partial atelectasis on the operated side. This patient had very large bilateral blebs and bullae with marked diminution of his respiratory reserve, and, on the tenth postoperative day, developed a tension pneumothorax on the unoperated side resulting in rapid deterioration to a

TABLE 4

SUMMARY OF RESULTS IN FOURTEEN OPERATIVE CASES

Indication for Surgery	Operative Procedure	Post-operative Complications	Late Complications	Deaths	Clinical Status
Group I: Bilateral bullae, severe diffuse obstructive emphysema (7 cases)	"Unroofing" technique (3 cases); pulmonary resection and excision of bullae (4 cases)	3 cases	Contralateral pneumothorax five years postoperatively (1 case); contralateral recurrent pneumonitis (1 case)	No operative deaths; (unknown cause, 3 years postoperatively after marked initial improvement, 1 case)	Initial improvement (all 7 cases); late improvement: 6 cases: 1 year —1 2 years—1 3 years—1 4 years—1 6 years—1 9 years—1
Group II: Unilateral bullae (7 cases)	Excision of bullae (3 cases); pulmonary resection (4 cases)	None	None	None	All 7 patients improved: 2 years—1 3 years—1 6 years—1 7 years—1 10 years—3

cyanotic, comatose, and virtually moribund state from which he made a dramatic recovery upon institution of closed thoracotomy drainage. Thereafter, he had a persistent air leak on the side of the spontaneous pneumothorax and formed a loculated empyema at the apex which necessitated rib resection drainage. Following this, he made a satisfactory recovery and was discharged from the hospital much improved from his preoperative condition.

The third patient was in extremely poor condition and had been on steroids preoperatively. Elective tracheostomy was done at the time of thoracotomy, but he ran a febrile postoperative course and developed late atelectasis of the lower lobe on the operated side three days following removal of the tracheostomy tube. An apical empyema pocket then appeared which promptly resolved after tube drainage. In this patient, also, slight enlargement of the air cysts on the unoperated side occurred.

There were no operative or postoperative deaths. Each of the remaining 11 patients had satisfactory postoperative convalescences.

Group I (table 4): In 7 of the 14 cases there was bilateral involvement. To the time of the present writing, surgery has been performed only on the side of maximal involvement in each of these patients. One of these patients developed a spontaneous pneumothorax on the unoperated side five years after surgery, and another has had recurrent pneumonitis on the unoperated side, presumably related to bronchopulmonary compression and impaired drainage secondary to an enlarging collection of air cysts in the upper lobe. Both of these patients are markedly improved over their preoperative status and have been advised to undergo excision of the remaining air cysts. One of the remaining 5 patients died three years following surgery after having been much improved during his early postoperative period. The ultimate cause of death is unknown, but he had severe obstructive emphysema with moderately extensive bullous formations on the unoperated side. The other 4 patients are continuing to lead normally active lives one, three, four, and six years postoperatively and, although the question of operating on the second side has been raised, each patient has continued to do so well that further surgery currently appears unjustified. In every patient the improvement obtained on the operated side has been maintained, both clinically and roentgenographically.

Group II (table 4): Although the remaining 7 patients had clinical evidence of diffuse ob-

structive emphysema, blebs and bullae were evident on only one side. In contrast to the marked ventilatory insufficiency which was uniformly present in each of the patients with bilateral air cysts, exertional dyspnea was noted in only 3 of the patients with unilateral cystic disease. Each of these patients had very extensive cysts producing significant compression of the pulmonary parenchyma, and each was improved following surgery. Improvement has been maintained to date for ten, seven, and three years in these 3 patients.

Two of the unilateral cyst group became symptomatic only with the development of spontaneous pneumothorax. Both patients have remained well for ten years following surgery, although one has recently experienced a minor episode of hemoptysis of indeterminate etiology.

One patient had moderate-sized air cysts but was asymptomatic when first seen. Two years later he began to note deep-seated chest discomfort, and roentgenograms revealed enlargement of the air cysts, with further compression of the adjacent middle and lower lobes. He had continued to smoke during this interval. Excisional surgery was performed, with considerable improvement, which has now been maintained for more than six years.

The final patient in this group was essentially asymptomatic but roentgenographically had an immense air cyst in the middle lobe which produced marked compression atelectasis of the lower lobe. The roentgenogram was unchanged during the first year of observation. Surgery was undertaken to avert the development of irreversible changes in the compressed lung. Following excision of the huge cystic mass together with multiple small blebs and bullae, the lower lobe expanded very satisfactorily. The roentgenogram has continued to be satisfactory and stable during the two years since surgery.

No complications were incurred among the 7 patients with unilateral blebs and bullae, and, to the present, no additional air cysts have developed.

Summary

The clinical features of large blebs and bullae were characterized by progressive debility from shortness of breath among middle-aged persons, predominantly males, who had been heavy smokers for many years.

Roentgenographically, differentiation of bullous formations from spontaneous pneumothorax and other varieties of cystic pulmonary disease and the evaluation of the degree of parenchymal compression by laminagrams, bronchograms, or angiocardiograms was stressed.

It has not been possible, employing current pulmonary function tests, to delineate indications for operative intervention on this basis alone. Although the vital capacity measurement is helpful when consistent with lung compression, the ultimate decision for surgery must rest primarily on clinical and roentgenographic findings. Some of the most dramatic operative results were obtained among patients exhibiting severe emphysema in conjunction with evidence of severe lung compression.

Criteria for operation were established, based upon the size of the bullous formations and the occurrence of significant pulmonary compression. Among 14 operative cases, 7 patients had bilateral bullous disease (*Group I*) and 7 had unilateral disease (*Group II*) associated with greater or lesser degrees of generalized pulmonary emphysema. All had unilateral surgery. There were three postoperative complications and one late death in *Group I* (three years postoperatively). The 6 survivors are all much improved up to nine years following surgery. In *Group II*, there were no complications, no deaths, and all patients are improved up to ten years following surgery. There has been no recurrence of disability in this series of cases.

Although the surgical techniques of resecting bullous lesions are not difficult to accomplish, careful judgment must be exercised in the selection of cases for operation, and a definite morbidity and complication rate should be anticipated, particularly in patients with bilateral bullous disease. The improvement achieved by operation may not be permanent, especially in patients who have diffuse pulmonary emphysema, but the palliative benefits appear to make the procedure worth while.

Sumario

La Asistencia Quirúrgica de las Grandes Flictenas y Bulas Pulmonares

Las características clínicas de las flictenas y bulas grandes de los pulmones se distinguieron por la debilidad gradual debida a falta de aliento entre las personas de edad media, predominantemente varones, que habían sido fumadores empedernidos por muchos años.

Radiográficamente, se recalcó la diferenciación de la formación bulosa del neumotórax espontáneo y otras variedades de las neumopatías quísticas y la justipreciación de la compresión parenquimatosa por medio de laminogramas, broncogramas o angiogramas.

No ha sido posible, empleando las pruebas corrientes de la función pulmonar, delinear las indicaciones para la intervención cruenta sobre esa base por sí sola. Aunque la medición de la capacidad vital es útil cuando resulta compatible con la compresión pulmonar, la decisión final en cuanto a la cirugía debe asentarse primordialmente en los hallazgos clínicos y radiográficos. Algunos de los resultados operatorios más dramáticos fueron obtenidos en enfermos que manifestaban enfisema grave junto con signos de intensa compresión pulmonar.

Se establecieron pautas para la operación, basadas en el tamaño de las formaciones bulosas y la existencia de importante compresión pulmonar. Entre 14 casos operatorios, 7 tenían enfermedad bulosa bilateral (*Grupo I*) y 7 unilateral (*Grupo II*), unida a enfisema pulmonar generalizado de mayor o menor grado. En todos se usó cirugía unilateral. Hubo tres complicaciones postoperatorias y una muerte tardía en el *Grupo I* (tres años postoperatoriamente). Todos los 6 sobrevivientes están muy mejorados hasta a los nueve años de la operación. En el *Grupo II*, no hubo complicaciones ni mortalidad y todos los enfermos están mejorados hasta a los diez años de la intervención. En esta serie de casos, no ha habido recurrencia de la incapacidad.

Aunque no es difícil ejecutar las técnicas quirúrgicas para la resección de las lesiones bulosas, hay que desplegar juicio esmerado en la selección de casos para la operación, y hay que esperar una tasa bien definida de morbidad y complicaciones, en particular en los enfermos que tienen afección bulosa bilateral. La mejoría lograda con la operación tal vez no sea permanente, sobre todo en los sujetos que tienen enfisema pulmonar difuso, pero parece que los beneficios paliativos hacen que valga la pena probar el procedimiento.

Resume

Conduite à tenir dans la chirurgie de grandes ampoules et vésicules pulmonaires

Les traits cliniques des grandes ampoules et vésicules ont été caractérisés par de la faiblesse progressive commençant par de l'essoufflement, chez des personnes d'un âge moyen, surtout chez les hommes, qui ont été de grands fumeurs depuis des années.

Au point de vue radiologique, les auteurs ont insisté sur les différences entre les formations vésiculeuses et le pneumothorax spontané, et d'autres variétés de maladies pulmonaires cystiques, et sur l'évaluation du degré de compression du parenchyme, à l'aide de laminogrammes, de bronchogrammes et d'angiogrammes.

On n'a pas pu, en employant les examens courants de la fonction pulmonaire, tracer les indications de l'opération chirurgicale sur cette seule base. Bien que la mesure de la capacité vitale soit utile quand elle se rapporte à la compression du poumon, la décision finale chirurgicale doit se baser en premier lieu sur les données cliniques et radiologiques. Les auteurs obtinrent quelques uns des résultats opératoires les plus saisissants parmi des malades présentant un emphysème sévère, en même temps que l'évidence d'une compression pulmonaire sévère.

Les auteurs établirent des critères opératoires basés sur la taille des formations vésiculeuses et l'apparition d'une compression pulmonaire notable. Parmi 14 cas opératoires, 7 malades avaient une forme vésiculeuse bilatérale (*groupe I*) et 7 une forme unilatérale (*groupe II*), associée à un degré plus ou moins important d'emphysème pulmonaire généralisé. Tous subirent une opération unilatérale. Il y eut trois complications postopératoires et une mort tardive dans le *groupe I* (trois ans après l'opération). Tous les 6 survivants furent améliorés jusqu'à neuf ans après l'opération. Dans le *groupe II*, il n'y eut ni complication, ni mort, et tous les malades s'améliorèrent jusqu'à dix ans après l'opération. Il n'y eut pas de rechutes d'incapacité dans ces séries de cas.

Bien que les techniques chirurgicales de résection des lésions vésiculeuses ne soient pas difficiles à pratiquer on doit exercer un jugement attentif dans la sélection des cas à opérer, et on devrait prévoir une morbidité définie et un taux de complications, particulièrement chez des malades ayant une maladie vésiculeuse bilatérale. L'amélioration obtenue par l'opération peut ne pas durer, spécialement chez les malades qui ont un emphysème pulmonaire diffus, mais les avantages palliatifs semblent rendre le procédé valable.

Addendum

Since submission of the manuscript, the writers have performed bilateral surgery in a 41-year-old aircraft engineer who was virtually totally incapacitated by diffuse bilateral bullous emphysema. Following an initial left thoracotomy with resection of bullae, an elective tracheostomy was performed. Postoperatively, the patient's maximal breathing capacity increased from 43 to 56 liters per minute and the timed vital capacity improved slightly, but a definite increase was observed in the size of the basilar bullae on the contralateral side. These were resected six months later, with a totally uncomplicated convalescence. Currently,

three months following his second procedure, he is asymptomatic and at work full time. This is an excellent result in a patient with severe diffuse emphysema and bilateral bullous lesions.

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ASSESSMENT OF OPERATIVE RISK IN THORACIC SURGERY[1]

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Introduction

In the past two decades great strides have been made in perfecting the techniques of thoracic surgery. In relatively young patients with normal cardiopulmonary function, the risk of thoracotomy has become negligible. However, in older patients and in patients with diminished cardiopulmonary reserve, surgery is still associated with a significant risk, especially when extensive pulmonary resections are performed. This report assesses the ability of certain preoperative tests to identify patients for whom thoracic surgery carries a greater than usual risk.

Methods

The correlation between mortality after surgery and performance on preoperative cardiopulmonary function tests was studied in adult patients undergoing thoracic surgery at the University of Chicago Clinics between January 1, 1956, and June 30, 1959. Included are patients who had pulmonary resections, cardiac surgery, and surgery involving the pleura, diaphragm, and mediastinal contents. Cases involving open heart surgery with hypothermia or cardiopulmonary bypass were excluded because of the difficulties in separating preoperative from operative factors in the genesis of complications in these patients. During the period under study, pulmonary function tests were not obtained routinely before thoracic surgery unless there was a clinical suspicion of excessive operative risk. Therefore, the present series is biased toward cases with high risk, and the mortality rates noted are not representative of the over-all experience at this institution. The pertinent clinical data in the 196 patients undergoing 199 thoracic surgical procedures are summarized in table 1.

In general, tests were performed immediately before surgery, but in several patients tests were obtained a few months preoperatively. In each such case, there was no reason to suspect that a change had occurred in the test results during the interval. Although the extent of testing varied, spirometry was performed in every case; measurements were made of the vital capacity and its subdivisions, the first-second vital capacity, and the maximal midexpiratory flow rate (1). In each case the maximal breathing capacity was determined, as was the air velocity index (2). The residual volume was determined in 105 cases and a nitrogen washout curve was obtained in 107 cases. Arterial oxygen saturation was measured by ear oximetry in 80 cases, and the resting diffusing capacity for carbon monoxide was determined in 38 cases. The methods employed and the standards of this laboratory have been described previously (3).

The following information was abstracted from the patient's records:

(*1*) The patient's age at the time of surgery, sex, type of surgery, and official diagnosis.

(*2*) The reported interpretation of the patient's preoperative chest roentgenogram (obtained in all cases) and electrocardiogram (obtained in all but 6 cases).

(*3*) An assessment of the amount of dyspnea present preoperatively, based on the clinical history. This was estimated as follows: grade 0—no dyspnea; grade 1—dyspnea after climbing more than one flight of stairs; grade 2—dyspnea after climbing one half to one flight of stairs; grade 3—dyspnea after any exertion; grade 4—dyspnea at rest.

(*4*) The patient's course after surgery.

Observations

Based upon the patient's course after surgery, each case was assigned to one of these two groups:

Group 1. Twenty-eight cardiorespiratory deaths. In 22 patients, death occurred during the early postoperative period, i.e., while the patient was still hospitalized, and was associated with complications involving the cardiovascular or respiratory systems. The remaining 6 patients in *Group 1* survived the early postoperative period, but died within six months of surgery with evidence of cardiorespiratory failure. The clinical findings in these 28 cases are summarized in table 2.

The specific cause of death in each case was difficult to determine even at postmortem examination (performed in 22 of the 28 fatalities). Twenty-four patients died from cardiorespiratory failure. Autopsy revealed tracheobronchitis in 7 patients, bronchopneumonia in 10, atelectasis in 10, left heart failure in 10, and 5 patients with cor pulmonale. Cardiorespiratory failure contributed significantly to the fatal outcome of the remaining 4 patients, two with cerebral infarcts and two with pulmonary emboli. Post-

[1] From the Department of Medicine, University of Chicago, Chicago 37, Illinois.

TABLE 1
CLINICAL INFORMATION ON PATIENTS IN STUDY

Number of patients in study		196
Male		127
Female		69
Number of operations		199
Age at time of operation		
Mean (*years*)		50.9
Range (*years*)		23 to 76
Operations performed		
Thoracotomy only		5
Pulmonary surgery		133
Biopsy, wedge or segmental resection	56	
Lobectomy (1 or 2)	46	
Pneumonectomy	27	
Resection of bullae, cysts, et cetera	4	
Cardiac surgery		30
Mitral valvulotomies	26	
Other	4	
Mediastinal surgery		21
Resections, explorations, biopsies	8	
Esophagectomy Esophagostomy Gastrectomy, et cetera	9	
Pericardial surgery	3	
Hiatal hernia repair	1	
Pleural surgery		10
Thoracoplasty, plumbage, et cetera	6	
Decortication	4	
Total operations		199

Operative diagnoses		
Tumor		110
Primary lung carcinoma	68	
Metastatic tumor of lung	19	
Hamartoma	3	
Pulmonary A-V fistula	3	
Bronchial adenoma	1	
Thymic tumor	5	
Mediastinal sarcoma	2	
Esophageal and gastric carcinoma	8	
Metastatic pleural tumor	1	
Infection		41
Tuberculosis	17	
Histoplasmosis	5	
Other granuloma	8	
Lung abscess	1	
Chronic pneumonitis	3	
Bronchiectasis	5	
Empyema	2	
Other pulmonary		11
Middle lobe syndrome	2	
Bronchial foreign body	1	
Cystic and bullous disease	5	
Silicosis	1	
Hemothorax, fibrothorax	2	
Cardiac and pericardial		33
Rheumatic heart disease	28	
Congenital heart disease	4	
Pericardial cyst	1	
Miscellaneous		4
Normal	1	
Hiatal hernia	1	
Esophageal stricture	1	
Hyperparathyroidism	1	
Total diagnoses		199

mortem findings included tracheobronchitis in 3, bronchopneumonia in 2, one with atelectasis, and left heart failure in 2 patients.

Group 2. One hundred and seventy-one patients without fatal cardiorespiratory complications. Four of these patients died in the early postoperative period, 3 of intrathoracic hemorrhage and one of renal failure following a transfusion reaction. The remaining 167 patients were either living at the last contact or had died following discharge from the hospital without evidence of cardiovascular or respiratory complications. Forty-seven patients died during the follow-up period of their primary disease or of another disease. Two patients were discharged to another physician and no follow-up data were available. Three patients were seen only once after surgery and 17 patients are no longer followed, although they were observed for at least six months after discharge. The remaining patients are followed in the outpatient clinics of this hospital.

RESULTS

Pulmonary Function Tests

The findings with spirometry and the other pulmonary function tests are summarized in table 3, correlating the preoperative test results with the course after surgery. In 39 patients, the vital capacity (VC) was less than 70 per cent of predicted. Eleven patients suffered fatal postoperative cardiorespiratory complications, yielding a fatality rate of 28 per cent. The fatality rate in patients with a vital capacity greater than 70 per cent of predicted was 11 per cent. There were 29 patients with a maximal breathing capacity of less than 50 per cent of

TABLE 2

GROUP 1: CARDIORESPIRATORY DEATHS

Early Deaths with Cardiorespiratory Complications				
Number of patients		22	Diagnosis	
Age (*years*) Mean		57.9	Lung carcinoma	12
Range		41 to 76	Bronchiolar carcinoma	1
Sex	Male	19	Adenoma	2
	Female	3	Bullous emphysema	1
Operation			Lung sarcoma	1
Biopsy		5	Pulmonary A-V fistula	1
Local resection		3	Actinomycosis	1
Lobectomy		5	Rheumatic heart disease	1
Pneumonectomy		5	Esophageal carcinoma	1
Gastrostomy		1	Gastric carcinoma	1
Gastroesophagectomy		1	Duration of postoperative survival	
Mitral valvulotomy		1	Mean	6.7 days
Pericardectomy		1	Range	1 to 26 days
Late Deaths with Cardiorespiratory Complications				
Number of Patients		6	Diagnosis	
Age (*years*) Mean		58.8	Lung carcinoma	6
Range		47 to 70	Duration of postoperative survival	
Sex	Male	6	Mean	2.8 months
Operation			Range	1.5 to 5 months
Biopsy		3		
Lobectomy		1		
Pneumonectomy		2		

predicted, including one patient too dyspneic to perform the test. Thirteen cardiorespiratory fatalities occurred in this group of 29 cases, a fatality rate of 45 per cent. An abnormal one-second vital capacity and a maximal midexpiratory flow rate were associated with fatality rates of only 16 and 21 per cent, respectively; but, when these findings accompanied a low vital capacity (less than 70 per cent of predicted), the fatality rate approximated that of patients with a low maximal breathing capacity (54 and 38 per cent). A similar result was obtained for the air velocity index. The fatality rate in the group of patients with an air velocity index of less than 0.8 was 20 per cent, compared with a fatality rate of 14 per cent for the entire series. In the group with a low air velocity index plus a low vital capacity, this rate was 53 per cent. (Results with maximal breathing capacity and vital capacity are depicted in figure 1, in which the excessive operative risk in subjects with a low vital capacity plus a low maximal breathing capacity is clearly indicated.) No patient with a vital capacity in excess of 120 per cent of predicted suffered a fatal cardiorespiratory complication.

In the group of 57 patients demonstrating air trapping during the maximal breathing capacity determination, 14 deaths occured, a fatality rate of 25 per cent. An increased fatality rate was noted with an increase in the residual volume to total lung capacity ratio (RV/TLC). Nine deaths occurred in the group of 25 cases with a RV/TLC greater than 50 per cent. The 36 per cent fatality rate in this group contrasts with the 8 per cent rate in patients with a RV/TLC of less than 40 per cent. Consideration of either the residual volume or the total lung capacity alone failed to reveal as striking a relationship between test result and fatality rate. The presence of an abnormal nitrogen washout curve was associated with a high fatality rate (47 per cent). Five of the 14 patients with abnormal peripheral oxygen saturation by ear oximetry suffered fatal cardiorespiratory complications while the demonstration of a low diffusing capacity (D_L) was associated with only two deaths in 11 patients.

Other Tests

The results of the other preoperative tests are also summarized in table 3. Twenty-one fatal cardiorespiratory complications developed in the group of 80 patients with abnormal electrocardiograms, yielding a 28 per cent fatality rate. The comparable rate was 6 per cent in patients

TABLE 3

RESULTS OF CARDIOPULMONARY FUNCTION TESTS

Finding	Number of Patients			Cardiorespiratory Death Rate
	Total	Group 1	Group 2	
				per cent
Total group	199	28	171	14
Pulmonary function tests				
Vital capacity				
>70% predicted	160	17	143	11
<70% predicted	39	11	28	28
Maximal breathing capacity				
>50% predicted	170	15	155	9
<50% predicted	29	13	16	45
One-second vital capacity				
>70%	131	17	114	13
<70%	68	11	57	16
<70% and vital capacity, <70% predicted	13	7	6	54
Maximal midexpiratory flow rate				
>100% predicted	127	13	114	10
<100% predicted	72	15	57	21
<100% predicted and vital capacity, <70% predicted	29	11	18	38
Air velocity index				
>0.8	134	15	119	11
<0.8	65	13	52	20
<0.8 and vital capacity, <70% predicted	17	9	8	53
Air trapping				
None	142	14	128	10
Slight to severe	57	14	43	25
Residual volume/total lung capacity				
10–39%	40	3	37	8
40–49%	43	7	36	16
50–72%	25	9	16	36
Residual volume				
70–129% predicted	32	7	25	22
130–200% predicted	53	6	47	11
>200% predicted	23	6	17	26
Total lung capacity				
<100% predicted	35	7	28	20
>100% predicted	33	4	29	12
N_2 washout curve				
Normal	88	12	76	14
Abnormal	19	9	10	47
7-minute alveolar N_2 concentration				
0.0–2.5%	92	18	74	20
>2.5%	13	4	9	31
Oximetry				
Normal	66	11	55	17
Abnormal	14	5	9	36
Diffusing capacity (CO)				
>15 cc./min./mm.Hg.	27	2	25	7
<15 cc./min./mm.Hg.	11	2	9	18
Electrocardiogram				
Normal	113	7	106	6
Abnormal	80	21	59	26
Heart block	3	0	3	0
Atrial fibrillation	7	2	5	29
Atrial abnormality	13	1	12	8
Premature contractions	11	2	9	18
Right ventricular hypertrophy	9	1	8	11
Left ventricular hypertrophy	3	1	2	33
Coronary artery disease	8	2	6	25
Nonspecific myocardial abnormality	26	12	14	46
Chest roentgenogram, heart size				
Normal	156	22	134	14
Cardiomegaly with left atrial enlargement	22	1	21	5
Cardiomegaly without left atrial enlargement	21	5	16	24
Dyspnea				
Grade 0—none	102	8	94	8
Grade 1—mild with exercise	39	6	33	15
Grade 2—moderate with exercise	49	9	40	18
Grade 3—severe with exercise	6	3	3	56
Grade 4—severe at rest	3	2	1	

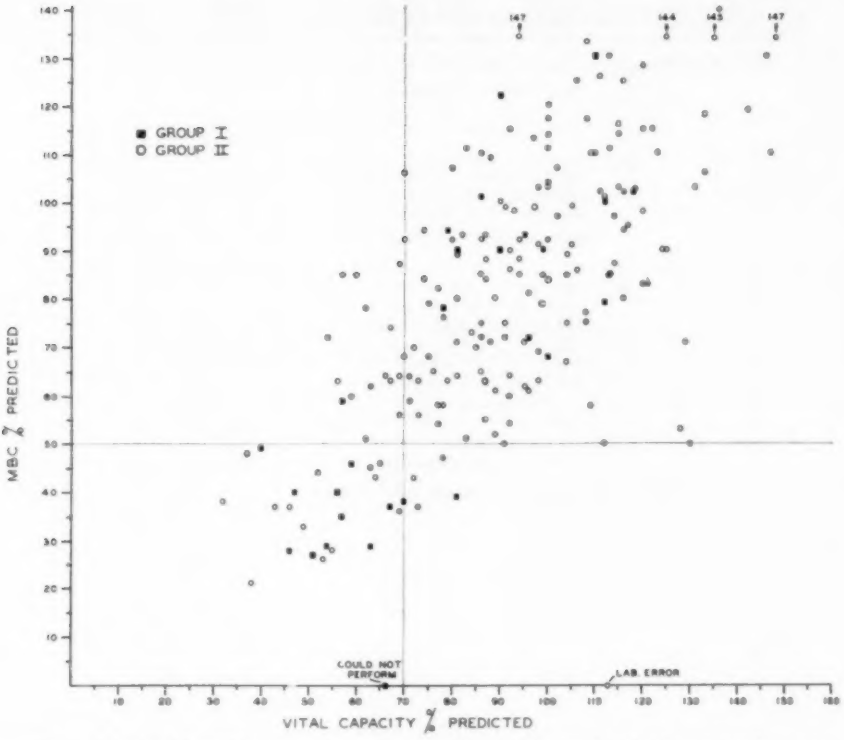

FIG. 1. Maximal breathing capacity plotted against vital capacity, both expressed as per cent of predicted:

Group 1—Cardiorespiratory deaths
Group 2—No fatal cardiorespiratory complications

with normal electrocardiograms. A detailed examination of the types of cardiographic abnormalities revealed the highest fatality rate (46 per cent) in the group showing nonspecific electrocardiographic abnormalities, although atrial fibrillation, left ventricular hypertrophy, and coronary artery disease (insufficiency or infarction) were also associated with excessive risk.

The roentgenographic demonstration of cardiomegaly without evidence of left atrial enlargement was associated with a 24 per cent fatality rate. In patients with rheumatic heart disease the demonstration of cardiomegaly was not correlated with an increased risk; the fatality rate in this group was 5 per cent. In 4 patients the radiologist noted the presence of congestive heart failure as evidenced by pulmonary congestion. All were patients with rheumatic heart disease. The only fatality following mitral valvulotomy occurred in one of these patients.

Dyspnea was present in 97 of the 199 patients. Twenty of the cardiorespiratory deaths occurred in this group. This represents a fatality rate of 21 per cent. The fatality rate in patients without dyspnea was 8 per cent. A total of 9 patients complained of severe dyspnea (grades 3 and 4), and 5 of this group suffered fatal complications.

Multiple Analysis

The serial application of two or more tests permitted the identification of groups with more significance with regard to the risk of surgery.

Of 21 patients with abnormal electrocardiograms and maximal breathing capacities of less than 50 per cent of predicted, 11 died. Fourteen patients with these findings were more than forty years old, and 10 of these 14 patients died.

Only 5 fatalities occurred in the group with

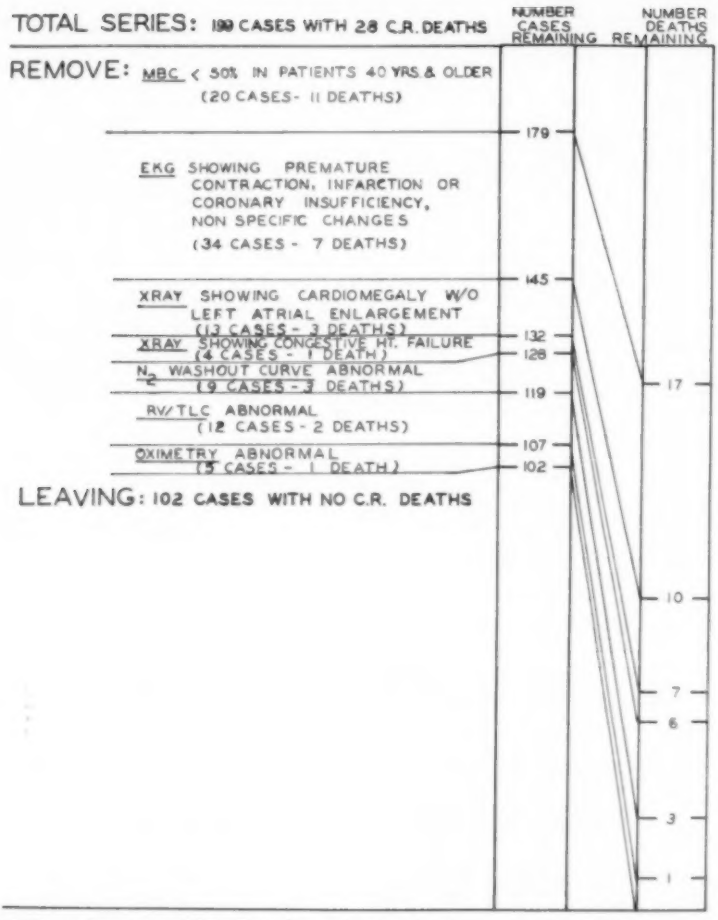
TOTAL SERIES: 199 CASES WITH 28 C.R. DEATHS
NUMBER CASES REMAINING
NUMBER DEATHS REMAINING
REMOVE: MBC < 50% IN PATIENTS 40 YRS & OLDER (20 CASES- 11 DEATHS)
179
EKG SHOWING PREMATURE CONTRACTION, INFARCTION OR CORONARY INSUFFICIENCY, NON SPECIFIC CHANGES (34 CASES - 7 DEATHS)
145
XRAY SHOWING CARDIOMEGALY W/O LEFT ATRIAL ENLARGEMENT (13 CASES - 3 DEATHS)
132
XRAY SHOWING CONGESTIVE HT. FAILURE (4 CASES - 1 DEATH)
128
N2 WASHOUT CURVE ABNORMAL (9 CASES - 3 DEATHS)
119
RV/TLC ABNORMAL (12 CASES - 2 DEATHS)
107
OXIMETRY ABNORMAL (5 CASES - 1 DEATH)
102
LEAVING: 102 CASES WITH NO C.R. DEATHS
17
10
7
6
3
1

FIG. 2. Test schema by which all cardiorespiratory deaths can be identified. The table lists the test criteria employed; the bar graphs depict the number of patients and deaths left after removal of each group with abnormal findings.

normal electrocardiograms and maximal breathing capacities in excess of 50 per cent. A total of 105 patients fell into this category, yielding a fatality rate of 5 per cent.

There were no fatalities in 39 patients who were found to have normal results in all tests performed.

Analysis of the test results in patients suffering fatal cardiorespiratory complications following surgery permitted the designing of a test schema which identified every patient who died following surgery. The schema is depicted in figure 2. The schema was designed to identify every fatality and yet include the fewest possible good-risk patients. Starting with the total series of 199 cases, the serial removal of patients with the abnormalities listed in figure 2 left a group of 102 patients with no fatal cardiorespiratory complications. All of the 28 cardiorespiratory deaths were included in the group of 97 cases identified by a combination of the maximal breathing capacity, electrocardiogram, chest roentgenogram, nitrogen washout curve, residual volume/total lung capacity ratio, and ear oximetry. The fatality rate in this group was 30 per cent.

The group of 102 cases cleared of risk differed from the total series of 199 only in minor clini-

TABLE 4
TEST INDICES

Test and Result	Test Sensitivity Index	Fatality Rate	Sum of Test Sensitivity Index and Fatality Rate
	per cent	*per cent*	
Test schema (*see* figure 2)	100	30	130
Electrocardiogram, any abnormality and maximal breathing capacity, <50% and age, >40%	36	72	108
Electrocardiogram, any abnormality	75	26	101
Dyspnea, any grade	71	21	92
Maximal breathing capacity, <50%	46	45	91
Nitrogen washout, abnormal	43	47	90
Electrocardiogram, nonspecific changes	43	46	89
Maximal breathing capacity, <50% with vital capacity, <70%	39	46	85
Air velocity index, <0.8 with vital capacity, <70%	32	53	85
Residual volume/total lung capacity, >50%	47	36	83
1-second vital capacity, <70% with vital capacity, <70%	25	54	79
Maximal midexpiratory flow rate, <100% plus vital capacity, <70%	39	38	77
Air trapping	50	25	75
Maximal midexpiratory flow rate, <100%	54	21	75
Dyspnea, severe	18	56	74
Diffusing capacity, abnormal	50	18	68
Oximetry, abnormal	31	36	67
Air velocity index, <0.8	46	20	66
1-second vital capacity, <70%	39	16	55
7-minute alveolar nitrogen, abnormal	18	31	49
Cardiomegaly without left atrial enlargement	18	24	42

cal details. The group of 102 was slightly younger (average age 48.1 years compared with 50.9 years in the total series), had fewer patients with malignancies (41.2 compared with 49.2 per cent), and had a greater proportion of female patients (42 compared with 36 per cent) and patients undergoing mitral valvulotomies (16.7 compared with 13.1 per cent). The proportion of pulmonary resections was nearly identical (70.5 and 69.5 per cent), as was the proportion of pneumonectomies (12.8 and 14.9 per cent).

Test Evaluation

The usefulness of a test in predicting fatal postoperative complications can be measured by two indices. The first, a measure of the test's ability to detect all patients who will die following surgery, will be referred to as the *test sensitivity index*. The test sensitivity index equals the percentage of total deaths in the group tested who showed the test result under consideration. The other index is simply the *fatality rate* in patients with any given test result. Considered together, these two indices are a measure of a test's over-all usefulness. In table 4 the calculated indices for some of these tests are listed in order of the diminishing sum of the two indices. The tests with a high total index are of three types: Those with a high sensitivity index (as the presence of any electrocardiographic abnormality or any degree of dyspnea) are good screening tests. They identify a majority of the fatalities but include many patients with benign postoperative courses. The tests with a high fatality rate (as the presence of severe dyspnea) identify few of the fatalities, but include very few good-risk patients. With certain tests (the test schema, the combination of electrocardiogram, maximal breathing capacity, and age and the maximal breathing capacity), both indices are relatively high.

DISCUSSION

The ideal assessment of operative risk would identify every patient who could safely tolerate surgery. This ideal is probably unattainable, but the present series of cases indicates that, on the basis of preoperative tests, considerable dis-

tinction can be made between patients with low and high operative risks. Patients in this series who died with cardiorespiratory complications in the operative or early postoperative period constitute a heterogeneous group with regard to preoperative diagnosis, operation performed, and types of postoperative complications. Nevertheless, it was found that these 28 patients could be identified by the preoperative tests.

The risk of surgery in these cases was more closely related to the preoperative test results than to the type or extent of surgery performed. Patients undergoing lung biopsy or local resection of pulmonary tissue suffered an 18 per cent fatality rate, whereas the rate in patients having lobectomy was 14 per cent. Pneumonectomy carried a 26 per cent mortality, and patients undergoing surgery upon organs within the mediastinum suffered a 13 per cent cardiorespiratory fatality rate. No deaths resulted from procedures upon the pleura and only one of 30 cardiac surgical patients suffered fatal complications. However, the latter patients were younger and otherwise healthy, with more normal preoperative test results.

The presence and severity of obstructive emphysema have been considered the main factors which determine the risk of thoracic surgery (4). The diagnosis and accurate assessment of early emphysema on the basis of physical examination is treacherous (5). Knowles (4) believes that the maximal breathing capacity is the single, most valuable preoperative test for detecting the presence of emphysema. In a group of 460 tuberculous patients subjected to various surgical procedures, Gaensler and associates (6) reported that 12 of the 13 postoperative deaths due to respiratory insufficiency occurred in patients with maximal breathing capacities of less than 50 per cent of predicted. The experience in the present series of cases is similar.

The ability to perform a maximal breathing capacity test is dependent upon many factors. The presence of airway obstruction is important and probably accounts for the general usefulness of this test in assessing emphysema. Although the maximal breathing capacity is often considered to be relatively independent of the lung volume, the relationship between it and the vital capacity in this series is apparent in figure 1. Other factors, such as cooperation, muscular strength, general debility, and the presence of pain with breathing, enter into a patient's performance on this test.

Other tests, such as the timed vital capacity (7), air velocity index (2), and maximal midexpiratory flow rate (1), have been shown to demonstrate airway obstruction more specifically than the maximal breathing capacity. However, in this series, these tests are poorer indices of surgical risk. Demonstration of airway obstruction by the one-second vital capacity, air velocity index, or maximal midexpiratory flow rate associated with a reduced vital capacity should reveal cases of emphysema as specifically as the maximal breathing capacity. This combination of findings failed to give an index of operative risk as valuable as the maximal breathing capacity. It is suggested that the maximal breathing capacity is a superior index of surgical risk, not because it specifically demonstrates the presence of obstructive emphysema, but because it is sensitive to many nonspecific factors in addition; these factors may be important in determining the course of recovery after thoracic surgery.

The value of the other tests of pulmonary function in predicting operability may be related to their ability to detect early obstructive emphysema. Gilson and Oldham (8) found that emphysema was best detected by an assessment of intrapulmonary gas mixing, by the maximal breathing capacity, and by the RV/TLC. In the present series of cases these were the pulmonary function tests most indicative of operative risk. Kukral and co-workers (9), in assessing operability in tuberculous patients, considered the presence of a RV/TLC in excess of 50 per cent indicative of "grade 4 risk." In the present series, more than one-third of the patients with that finding suffered fatal cardiorespiratory complications after surgery.

Abnormalities of peripheral oxygen saturation by ear oximetry and reduced diffusing capacity were seen infrequently in the present series, and their importance in preoperative evaluation is difficult to assess. The relatively low mortality rate associated with a decreased diffusing capacity is of interest in the light of the recent demonstrations by Dietiker and associates (10) that the diffusing capacity may be appreciably reduced after various thoracic surgical procedures.

The presence of dyspnea of any grade in this series was a nonspecific index of surgical risk

Gaensler and co-workers (6) reported a poor correlation between the presence of preoperative dyspnea and the development of postoperative pulmonary insufficiency. Badger (11) urged the careful preoperative testing of patients in whom the degree of dyspnea seemed inconsistent with an initial clinical impression of the patients cardiopulmonary reserve. The experience gained from the present series of patients indicates that, in the presence of severe dyspnea, surgery carries with it a very high risk (5 deaths in the 9 patients).

The association between increased surgical risk and certain types of organic heart disease is well documented. Levine (12), in a study of 414 patients with organic heart disease subjected to various surgical procedures, found the risk of fatal postoperative complications to be increased in the presence of coronary artery disease and/or congestive heart failure. The risk associated with valvular disease and/or auricular fibrillation was not great. The association between coronary artery disease and fatal postoperative complications, especially thromboembolism, has been repeatedly reported (13–15). Wang and Howland (15), in a study of elderly surgical patients, found a correlation between the occurrence of premature contractions and operative risk. Findings in the present study are in accord with these previous observations.

Of special interest is the group of 26 patients who revealed "nonspecific abnormalities" on their electrocardiograms. Nearly one half of these patients suffered fatal complications. In 12 of the 26 cases the pulmonary function tests were diagnostic of severe obstructive emphysema. The electrocardiographic changes were suggestive, but not diagnostic, of right ventricular hypertrophy. Seven of the 12 patients with severe emphysema plus nonspecific electrocardiographic abnormalities suffered fatal cardiorespiratory complications. In these patients, it is probable that the electrocardiographic changes indicated some cor pulmonale prior to surgery.

In the remaining 14 patients with nonspecific electrocardiographic changes, the preoperative pulmonary function tests were relatively normal. Five deaths occurred in this group. Two of the 5 patients suffered cerebral vascular accidents, but postmortem examinations revealed pulmonary asbestosis in one case and obstructive emphysema in the other. In one case, the nonspecific abnormality was associated with widespread bronchiolar carcinoma. In another patient whose nonspecific electrocardiographic abnormality was the only deviation from normal on the preoperative tests, the course after surgery was compatible with the development of cor pulmonale. In these last 4 cases, it seems likely that the preoperative nonspecific electrocardiographic changes were associated with underlying right heart strain. The remaining cardiorespiratory death in a patient with nonspecific electrocardiographic changes occurred in an elderly diabetic in whom the presence of coronary artery disease was suggested. Death was associated with thrombophlebitis and possible pulmonary embolization.

Thus, in 11 of the 12 deaths associated with nonspecific electrocardiographic changes, there is reason to believe that this finding was associated with some underlying tendency to cor pulmonale which may have "set the stage" for the postoperative complications. Myers, Klein, and Stofer (16) demonstrated the difficulties attending the electrocardiographic diagnosis of right ventricular hypertrophy. The importance of nonspecific electrocardiographic changes in patients in the present study is stressed in assessing right heart status.

The greatest potential value of the tests studied here seems to be in the simultaneous use of more than one test in analyzing a group of patients. The finding of normal results in all tests performed gave great assurance of a safe postoperative course (no deaths in 39 such patients). In the group of 105 patients with normal electrocardiograms and maximal breathing capacities in excess of 50 per cent of predicted, the fatality rate was quite low (5 per cent). In contrast, patients with abnormal results in these tests, who in addition were more than forty years of age, suffered a fatality rate of 71 per cent (10 deaths in 14 patients).

It is of interest that a schema can be designed which identifies every postoperative fatality in this series. The design of this schema is based upon a desire to include all fatalities in the smallest possible total group. The result is an artificial group of test criteria, applicable to this series of cases, and probably not of general usefulness. All 28 cardiospiratory deaths were identified by the schema, but they were grouped with 69 cases with a benign postoperative course. If this schema had been employed in selecting patients for surgery, these 69 patients would

have been prevented from having needed operations.

None of the tests studied here are specific indices of operative risk, or even specific for the diagnosis of any disease. No test of preoperative function can take into consideration the amount of tissue which will be removed at surgery or made nonfunctional by the development of a postoperative pleural effusion or other complication. These objections apply to any preoperative test which might be employed. The most important indices of operative risk may not have been utilized in the present study. The prognostic value of the preoperative pulmonary artery pressure (17) and the ballistocardiogram (15) have previously been demonstrated. Other tests, which might prove to be of prognostic value, but which were not obtained routinely, include the measurement of pulmonary compliance, airway resistance, blood pH, carbon dioxide pressure (pCo_2), and physiologic dead space.

Summary

A study was undertaken in a group of patients undergoing 199 thoracic surgical procedures to assess the value of certain preoperative cardiopulmonary function tests in predicting fatal postoperative complications. Despite the limited number of tests studied, each of 28 patients who developed fatal complications after surgery had evidence of pre-existing disease involving the cardiovascular or respiratory system. Surgery in patients with normal test results was associated with negligible risk.

The preoperative tests employed in this study were of unequal value in predicting the risk of surgery. The results of the electrocardiographic and the maximal breathing capacity tests, readily available to any physician, were of greatest value in predicting the outcome after surgery. Test results indicating the presence of significant chronic obstructive emphysema were most frequently associated with fatal postoperative complications. By serial application of two or more tests, groups of patients with high risk could be defined. The value of such multiple tests in predicting operative risk was greater than any single test.

Although it was possible to identify all cardiorespiratory fatalities on the basis of the preoperative tests, there was no way to differentiate between the 28 patients who died and 69 patients with the same findings who did not die. Further study may make such differentiation possible. Currently, preoperative tests indicate the presence of cardiac or pulmonary disease and give an estimate of the risk of surgery in the face of such disease.

Sumario

Valoración del Riesgo Operatorio en la Cirugía Torácica

Este estudio fué emprendido en un grupo de enfermos sometidos a 199 procedimientos de cirugía torácica para determinar el valor de ciertas pruebas preoperatorias de la función cardiopulmonar en la predicción de complicaciones postoperatorias letales. A pesar del limitado número de pruebas estudiadas, cada uno de los 28 enfermos que manifestaron complicaciones letales después de la cirugía tenía signos de patología preexistente que afectaba el aparato cardiovascular o el respiratorio. En los enfermos que mostraron resultados normales en las pruebas, la cirugía se acompañó de riesgo menospreciable.

Las pruebas preoperatorias empleadas en este estudio mostraron valor desigual en lo tocante a predecir el riesgo de la cirugía. Los resultados del electrocardiograma y de la capacidad respiratoria máxima, pruebas estas al fácil alcance de cualquier médico, fueron las de mayor valor para predecir el desenlace de la cirugía. Los resultados de las pruebas que indicaban la presencia de enfisema oclusivo crónico de importancia fueron las que se vincularon más frecuentemente con complicaciones postoperatorias letales. Con la aplicación seriada de dos o más pruebas, cabría definir los grupos de enfermos que entrañan más riesgo. El valor de esas pruebas múltiples en la predicción del riesgo operatorio fué mayor que el de ninguna prueba aislada.

Aunque fué posible identificar todas las muertes cardiorrespiratorias a base de las pruebas postoperatorias, no hubo modo de diferenciar los 28 enfermos que fallecieron de los 69 que tenían los mismos hallazgos y no fallecieron. En resumen, las pruebas preoperatorias indican la presencia de patología cardíaca o pulmonar y ofrecen una idea del riesgo de la cirugía cuando existe tal patología.

Resume

Evaluation du danger opératoire en chirurgie thoracique

L'auteur entreprit une étude parmi un groupe de malades subissant 199 interventions chirurgicales thoraciques, pour déterminer la valeur d'examens pré-opératoires de certaines fonctions car-

dioputmonaires, pour prédire les complications post-opératoires fatales. Malgré le nombre limité des examens étudiés, chacun des 28 malades qui développèrent des complications fatales après chirurgie, montra une pathologie pré-existente intéressant le système respiratoire ou cardiovasculaire. La chirurgie chez des malades ayant des résultats d'examens normaux fut associée à un danger négligeable.

Les examens pré-opératoires employés dans cette étude furent d'une valeur inégale dans la prédiction du danger chirurgical. Les résultats d'electrocardiogramme et la capacité maxima de respiration, examens faciles à obtenir pour n'importe quel médecin, furent de très grande valeur pour prédire l'avenir après chirurgie. Les résultats d'examens indiquant la présence d'un emphysème obstructif chronique important furent le plus fréquemment associés aux complications fatales postopératoires. Grace à l'emploi en séries de deux, ou plus, examens, on put établir des groupes de malades courant un grand danger. La valeur de tels examens multiples pour prédire le danger opératoire fut plus grande qu'un seul examen.

Bien qu'il soit possible d'identifier tous les cas fatals cardiorespiratoires en se basant sur les examens pré-opératoires, il n'y eut pas moyen de faire la différence entre les 28 malades qui moururent et les 69 malades ayant les mêmes tableaux cliniques qui ne moururent pas. Une étude ultérieure peut rendre possible une telle différenciation. A l'heure actuelle, les examens pré-opératoires indiquent la présence d'une pathologie cardiaque ou pulmonaire et donnent une estimation du danger opératoire dans le cas d'une telle pathologie.

Acknowledgment

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PULMONARY CALCIFICATIONS AND HISTOPLASMOSIS[1]

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INTRODUCTION

During the past fifteen years much evidence has been accumulated from many and widespread sources to show that histoplasmosis occurs in man and in a variety of other animals. Not only has the organism, *Histoplasma capsulatum*, produced obvious acute and chronic disease in patients, but methods such as skin testing and tissue examination show that most infections go unnoticed and then leave little evidence behind. Schwarz and Baum (1) have given an excellent review of this phase of our progress. But history is not yet through with this microorganism. It plays a significant role in our understanding of the problems of pulmonary calcifications, and anyone reviewing the literature on this subject is treated again to a beautiful pattern of progress which has unfolded in the recent past.

REVIEW OF LITERATURE

Following Ghon's work on pulmonary calcifications in children (2), emphasis was placed on tuberculosis as the cause of these lesions in both old and young alike. However, as early as 1926, Opie and McPhedran pointed out the occurrence of "primary complexes" in children with negative tuberculin reactions (3), and Sayers and Meriwether had suggested in 1932 that fungous infection might be the cause of some miliary pulmonary calcifications (4). Bloch in 1943 presented a re-evaluation of the Ghon tubercle and pointed out that many calcified foci in adult lungs were remnants of the reinfection type of tuberculosis acquired during the adult age (5).

The ring began to tighten in 1949 when Meleney roughly mapped out the endemic area of histoplasmosis (6) and, in 1945, Long and Stearns observed an increased incidence of calcifications in the chest films of Army recruits from this same area (7). Gass and associates, in 1943, reported a marked discrepancy in the correlation of pulmonary calcifications and positive tuberculin tests in a group of children from middle Tennessee (8). Smith (9) first suggested in this same year that *Histoplasma capsulatum* might be the etiologic agent causing pulmonary calcifications in the endemic areas. Work showing the correlation between histoplasmal infections and residual pulmonary calcifications had to await the development of a satisfactory Histoplasma skin sensitivity test. This in turn was dependent on adequate cultures of the organism. DeMonbruen (10) and Hansmann and Schenken (11) had already obtained the first cultures of *Histoplasma capsulatum* in 1933 and 1934. A satisfactory histoplasmin skin test was developed in 1945 (12, 13). The classic works of Christie, Palmer, Furcolow, and others soon followed, showing the relationship of pulmonary calcifications in endemic areas and positive histoplasmin skin tests (13–19).

Although some objections were made to the conclusions derived from the use of histoplasmin tests (20, 21), the statement by Furcolow was generally accepted that "tuberculosis is an exceedingly infrequent cause of disseminated pulmonary calcification. Histoplasmosis or some closely related infection is the cause in most cases" (13). These investigators had done their work so well that it became necessary for the average physician to be reminded that miliary pulmonary calcifications could represent healed tuberculosis (22, 23).

In spite of the epidemiologic evidence produced, the desire for more conclusive proof of the etiology of pulmonary calcifications was stronger than ever, since at no time had Koch's postulates been satisfied. The statement by Sontag and Allen (24) in 1947 was timely: "Pulmonary calcifications are apparently non specific reactions to a variety of organisms. Cutaneous sensitivity tests and procedures other than roentgenologic must be employed to make an etiological diagnosis."

With improvements in techniques it was possible by 1948 to develop complement-fixation tests of human serum which gave reliable results in the acute stage of histoplasmal infection (25–28). Although serologic tests have been of much value in institutions treating active pulmonary disease (29), thus far the usefulness of these procedures for further inquiry into the etiology of pulmonary calcifications has been limited. However, search for new procedures continues in this field. The hemagglutination test is an example of one of the procedures which may prove significant for the epidemiologist as well as for the clinician (30).

In the histochemical phase, Gomori (31) developed the technique of staining glycogen and mucin by the methenamine silver method in 1946. In the same year, McManus reported the use of periodic acid oxidation followed by treatment with Schiff's fuchsin-sulfurous acid for staining mucin (32). This periodic acid-Schiff stain was later used to demonstrate many tissue substances, including

[1] From the Laboratory Service, Veterans Administration Medical Teaching Group Hospital, Memphis 15, Tennessee.

fungi (33). Gridley developed a similar stain, using chromic acid as the oxidant instead of the stronger periodic acid (34), thus supposedly eliminating the positive staining of tissue elements. Grocott (35), nine years after Gomori's work with methenamine silver, suggested the use of this stain with a hematoxylin and eosin background in identifying the smaller fungi such as *Histoplasma capsulatum*.

With the availability of these methods, steps toward more conclusive proof of the etiology of some of the pulmonary calcifications soon followed. Schwarz and associates (36) in 1955, in their report of increased incidence of splenic calcifications in the endemic area of Cincinnati, showed that 47 per cent of 40 spleens with "typical foci" contained structures resembling *Histoplasma capsulatum* organisms with the Gridley stain. High (37) had previously shown in 1946 a greater incidence of positive histoplasmin skin tests in 20 cases of splenic calcification, thus indicating that benign histoplasmosis could be a systemic disease. Later in the same year Straub and Schwarz (38) reported finding stainable fungi consistent with *Histoplasma capsulatum* in the primary complexes of 67 per cent of 105 consecutive autopsies performed in Cincinnati in cases other than known histoplasmosis or tuberculosis. The Gridley and periodic acid–Schiff stains were used. Cultures of 40 calcified foci were performed, all of which were negative. Other reports were given, however, such as that by Young and co-workers (39), urging caution in basing conclusions on such stains since those writers had been unable to duplicate the work of Schwarz using the periodic acid–Schiff and Gridley stains on splenic calcifications in another endemic area.

Nevertheless, investigation continued showing surprisingly high incidences of pulmonary calcifications with structures resembling fungous organisms (coccidioidomycosis and histoplasmosis in the respective endemic areas) (40), especially when the methenamine silver stain was used.

The investigations then branched into other phases of lung pathology. For instance, it is said that most broncholiths originate by erosion of calcified parabronchial and paratracheal lymph nodes into the lumen of the associated structure (41). It is no surprise, then, to find reports in the literature, such as those of Baum, Bernstein, and Schwarz (42), in which two patients with broncholiths showed organisms resembling *Histoplasma capsulatum*. Weed and Anderson presented twelve cases of broncholithiasis, five of which revealed organisms resembling *Histoplasma capsulatum*; eight revealed organisms resembling Nocardia in the concretions (43). The methenamine silver stain was used.

At the present time the "special stain" period of studying pulmonary calcifications continues, but even now possibly better and more specific tests for identifying organisms in calcified and noncalcified granulomas are coming to the fore. Gordon (44) reported in 1959 on the use of the fluorescent staining of *Histoplasma capsulatum* but, to the writers' knowledge, the use of this method with pulmonary calcifications has yet to reach the literature.

The writers believe that any investigation such as that of Schwarz (38), which reports that organisms resembling *Histoplasma capsulatum* were observed in pulmonary calcifications in 67 per cent of 105 consecutive autopsy cases, is highly significant to the medical profession, particularly to physicians treating diseases of the lung in endemic areas. Segal and associates (45) at the Mayo Clinic report finding organisms resembling *Histoplasma capsulatum* or *Coccidioides immitis* in 55.9 per cent of 138 surgically excised pulmonary granulomas using the methenamine silver stain. This tends to substantiate Schwarz's work on autopsy specimens in Cincinnati but, to the present writers' knowledge, the reports on autopsy specimens from the Cincinnati area have not been duplicated in any other locale within the "Histo belt." For this reason such a report is submitted below.

Materials and Methods

One hundred consecutive cases of calcified foci in lung parenchyma and/or hilar nodes were obtained from autopsies performed at the Kennedy Veterans Administration Medical Teaching Group Hospital, Memphis, Tennessee. Cases of known tuberculosis, histoplasmosis, or other pulmonary diseases were not excluded, in the hope of obtaining a true representation of the incidence of pulmonary calcified foci containing organisms resembling *Histoplasma capsulatum* in a given autopsy series. No limitations were placed on the size or type of lesions used in this series. The only requirements were that such lesions represent the end result of an inflammatory reaction containing some calcium and that they be located within the lungs or the corresponding regional lymph nodes. The series contained typical Ghon complexes (figure 1), miliary lesions (figure 2), massive calcified nodes, and all types in between these extremes. The presence of most of these was obvious, and no difficulty was encountered in locating such foci. In some instances, however, a careful search by serial sectioning and palpation of each slice of lung tissue was required to find the smaller lesions.

The calcified foci were bisected under relatively sterile conditions. One-half of each was ground in a Tenbroeck tissue grinder, then cultured on Sabouraud and Thompson media at room temperature and at 37°C., respectively, for four weeks. The other half of each lesion was fixed in 10 per cent formalin for twenty-four hours, then decalcified for twelve hours in a solution containing concentrated 2.5 per cent hydrochloric acid and 10 per cent formic acid. The specimens were washed in tap water for six to eight hours, processed in a routine manner, and stained with hematoxylin and eosin alone and with methenamine silver using a hematoxylin and eosin background (figures 3, 4). Two slides for each stain were obtained, and every slide was examined microscopically by each of the writers before a final conclusion was reached. Any case revealing organisms resembling *Histo-*

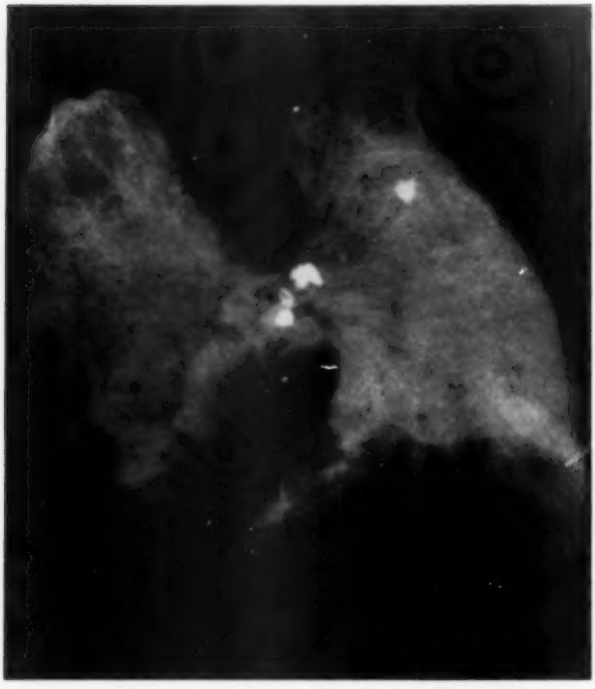

FIG. 1. Roentgenogram of left lung illustrating a typical "primary Ghon complex." The lymph nodes here were positive on tissue examination for organisms resembling *Histoplasma capsulatum*.

plasma capsulatum (1 to 5 μ oval cells with dark staining capsules and dark to clear centers) (46) was recorded as positive. The spleen from each autopsy was serially sectioned in one-eighth-inch slices and all calcified foci in this organ were collected in a separate series (figure 5). These lesions were decalcified and stained in the same manner as that described above, but no cultures were performed.

Blood was drawn from the left ventricle in each case and the specimen was used in the following serologic tests for histoplasmosis: complement-fixation in both yeast and mycelial phases; collodion agglutination; and hemagglutination.

At the time of the autopsy the occupation and home address of each subject was recorded. The occupation given best represents the type of work and surroundings in which the individual was employed for the longest period of his active years of life.

RESULTS

Incidence: The total number of autopsies required to obtain 100 consecutive cases of calcified pulmonary lesions was 111, thus revealing that at least 90 per cent of all patients autopsied at this hospital during this period had calcified pulmonary foci.

Fifty-eight of these 100 cases consisted of the "typical" primary or Ghon complex. The remainder showed multiple (two or more) calcifications in one or both lungs plus the usual calcifications of the hilar lymph nodes. No case of splenic calcifications only was found.

In 71 of the 100 cases studied with the methenamine silver stain, organisms resembling *Histoplasma capsulatum* were found in one or more foci. Two of the 71 cases were positive for such organisms in splenic nodules only. Therefore, at least 63.9 per cent of all autopsied cases examined during this period contained at least one calcified lesion either in the lungs, respiratory nodes, or spleen which showed organisms resembling *Histoplasma capsulatum* with special staining.

Thirty-nine of the 58 "typical" primary complexes revealed organisms resembling *Histo-*

FIG. 2. Roentgenogram illustrating a typical miliary pattern of pulmonary calcifications. Many of the nodules seen here contained organisms resembling *Histoplasma capsulatum* on tissue examination.

plasma capsulatum, and 30 of the 42 cases of multiple calcifications showed organisms resembling *Histoplasma capsulatum* with the special stains.

Thirty-five of the 100 cases of calcified pulmonary foci revealed one or more calcified nodules in the spleen. Seven of these nodules contained organisms resembling *Histoplasma capsulatum* when stained with methenamine silver.

Evidence of any inflammatory activity in or about these foci was noticeably absent. In fact, in not one single case could even a slight degree of peripheral inflammatory activity be demonstrated.

Epidemiologic findings: Each dot on the map in figure 6 represents the home region of each of the 71 patients with positive calcifications. It may readily be seen that almost all of the subjects lived within the Mississippi Valley and that the majority resided in the area surrounding Memphis commonly known as the "mid South."

The occupations were divided into three general classifications: those requiring the subject to be indoors; those in which the subject remained outdoors but performed duties not of an agricultural nature; and those in which the subject had an agricultural environment. Thirty-seven of the 100 had "indoor" occupations, 37 had "outdoor" occupations not of an agricultural nature, and 26 were employed in an agricultural occupation. Of the 37 with "indoor" occupations, 27 were recorded as positive for Histoplasma organisms in the tissue examinations. Twenty-seven of the 37 with "outdoor" nonagricultural occupations were positive in the tissue examinations, and 17 of the 26 with agricultural occupations were positive for Histoplasma organisms in the tissue examinations.

Bacteriologic findings: Only one of the 100 cases was positive by culture for *Histoplasma capsulatum*. This was a subject who had extensive bilateral pulmonary and hilar node calcifications plus splenic nodules. The tissue exami-

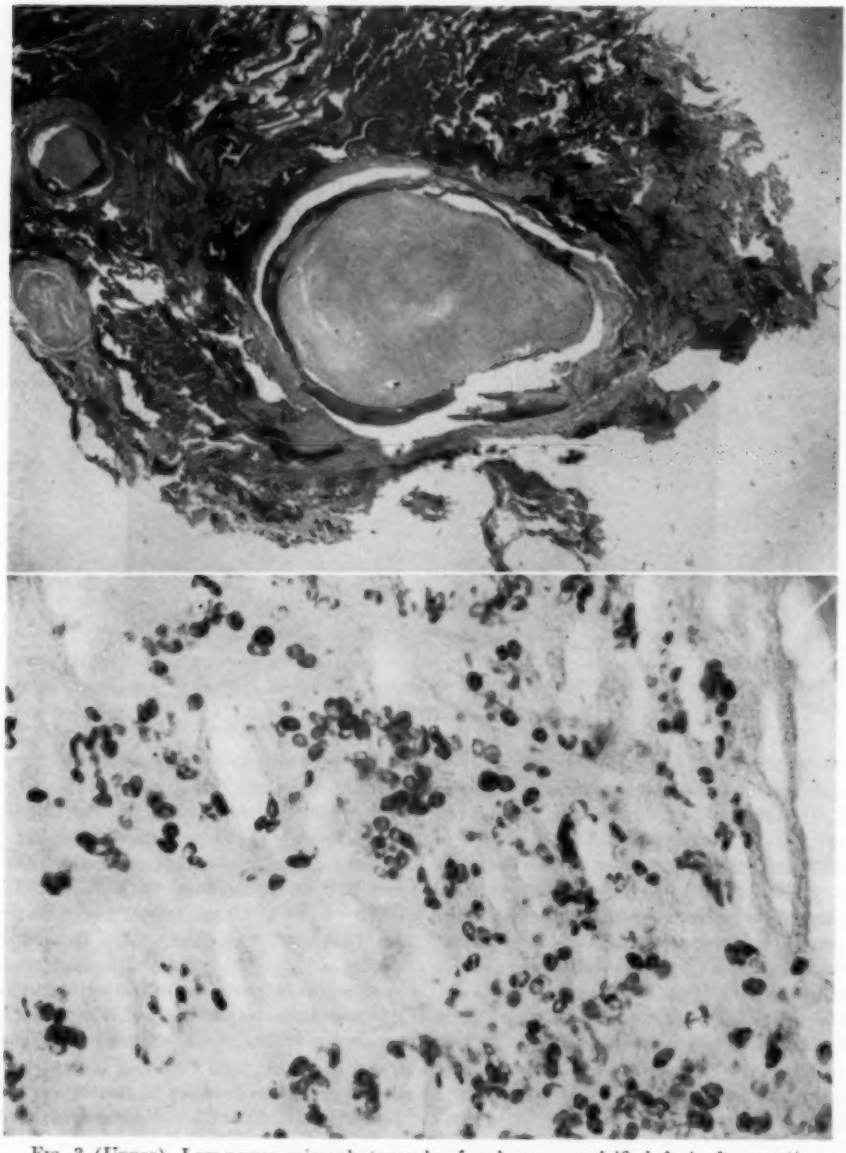

FIG. 3 (Upper). Low-power microphotograph of pulmonary calcified foci after routine processing and hematoxylin and eosin stains. The largest focus revealed organisms resembling *Histoplasma capsulatum*. Note the absence of active inflammation.

FIG. 4 (Lower). High-power microphotograph illustrating the appearance of the organisms resembling *Histoplasma capsulatum* in a partially calcified pulmonary lesion stained by the methenamine silver method. Note the tendency to cluster in small groups.

FIG. 5. Photograph of gross specimen illustrating several small calcified splenic nodules typical of those found during the study. These nodules were positive for organisms resembling *Histoplasma capsulatum* on tissue examination.

nations of these foci were negative for the organism. The serologic studies on this case were also negative.

Serologic findings: In none of the cases in the series was the reaction positive for Histoplasma, using the complement-fixation tests (yeast and mycelial phases) and the collodion agglutination tests for histoplasmosis. However, there were 7 positive reactions with the hemagglutination test. Four of these showed a titer of 1:8; 2, a titer of 1:16; and one, a titer of 1:32. Two of the four cases with 1:8 titers were positive in the tissue examinations; both cases with 1:16 titers were positive in the tissue examinations, and the single case with the 1:32 titer was negative in the tissue examination.

DISCUSSION

It is apparent from the figures given that the results of this study parallel to a considerable degree the work done in Cincinnati by Straub and Schwarz (38). After the beginning of the study it seemed that the number of calcified foci and organisms found was in direct proportion to the diligence with which a search was made for small nodules in the lungs and for organisms in the tissue sections. It should be pointed out, however, that only one to two sections of a nodule were examined since it was desired to get an incidence which would be expected to be found by methods used in a routine study of tissues. No doubt a somewhat higher incidence could have been obtained by serial or step sections of these nodules. In many, the identifiable organisms seemed to cluster in one or more foci in the nodule.

The lack of correlation between the presence of *Histoplasma capsulatum* and the type of calcified lesion in which they were found ("typical" primary vs. multiple calcifications), as shown in this study, would tend to negate any effort to classify by roentgenographic appearance pulmonary calcified lesions into etiologic groups, i.e., those due to histoplasmosis, tuberculosis, or coccidioidomycosis, et cetera.

The geographic data shown are significant only in that only one of the individuals in this series had come to this hospital for his final illness from a nonendemic area. Therefore, the figures given represent a true study of the problem as seen in this particular region.

It should be understood that the lack of correlation between the incidence of organisms found and the occupation of the individual in no way contradicts previous studies showing the high incidence of *Histoplasma capsulatum* or-

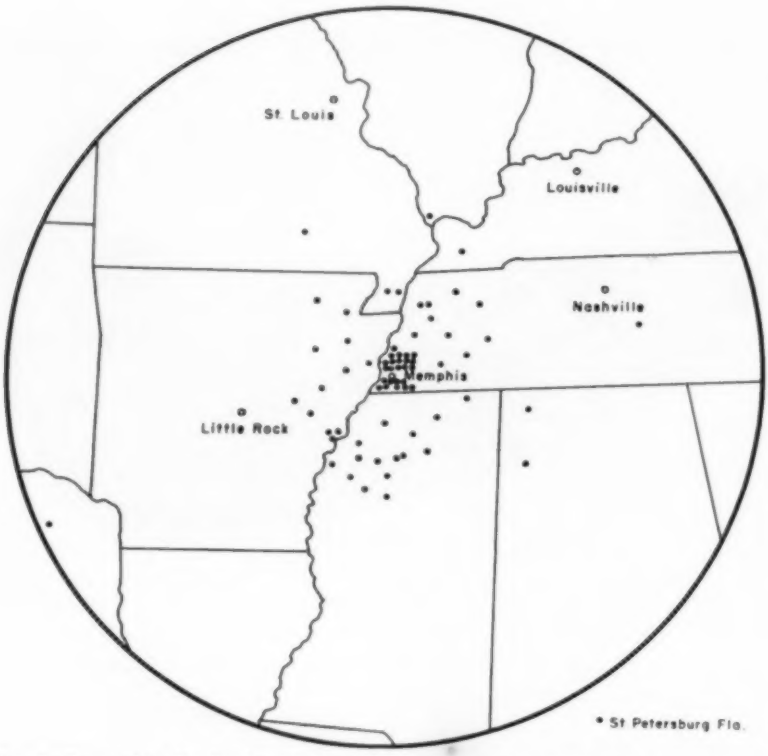

FIG. 6. Geographic distribution of the 71 patients with foci positive for organisms resembling *Histoplasma capsulatum* on tissue examination.

ganisms found in such agricultural environments as chicken yards and rotting tree stumps. It should be kept in mind that most males of this general age group (World War I and World War II veterans) from this region have most likely had intimate contact with an agricultural environment at some period in their lives. The disease certainly may be contracted after very short exposure in an area where the soil contains the mycelial phase of the organism. Obviously, to obtain a true correlation between incidence of calcifications with organisms and the activity of the individual a detailed environmental history from birth would be required. Edwards and Klaer (47) and Manos and associates (48) have pointed out that the geographic area where a man lives is the important factor and not what his occupation is or what his socio-economic status happens to be.

The routine serologic studies in this report merely confirm the general impression held by most authorities that these tests are of value only in the active phases of the disease. The hemagglutination test, although not showing a striking correlation, did reveal a number of positive cases, 4 of which also showed organisms in the tissue examinations. Certainly, further investigation is warranted with this procedure.

The complete absence of any inflammatory activity in this series fits well with the bacteriologic findings. It is highly unlikely that a calcified focus of the sort observed could ever "break down" and produce a recurrent local or disseminated disease due to *Histoplasma capsulatum*. Only one in a hundred cases yielded a culture positive for *Histoplasma capsulatum*. However, the writers feel justified in emphasizing to the physicians treating chest diseases in this region the frequency of *Histoplasma capsulatum* as the cause of granulomatous reactions in the lungs of their patients.

Summary

A brief history of the study of pulmonary calcifications is given.

A series of 100 consecutive cases of pulmonary and nodal calcifications from 111 autopsies was studied. In 71 (63.9 per cent) of the 111 autopsies, organisms resembling *Histoplasma capsulatum* were found in the calcific foci stained by the methenamine silver method. Thirty-five of the 100 patients also had had splenic calcifications, and 20 per cent of these revealed organisms resembling *Histoplasma capsulatum*. Ninety-nine per cent of the subjects studied lived in the area of the mid South. No correlation could be shown between the incidence of positive nodules and the occupation of the individual.

All complement-fixation and collodion tests on blood obtained at autopsy were negative for antibodies against *Histoplasma capsulatum*. The hemagglutination test is worthy of further study in such cases as these. In one case a positive culture for *Histoplasma capsulatum* was found, but cultures in the other 99 were negative.

Sumario

Las Calcificaciones Pulmonares y la Histoplasmosis

Se ofrece una breve reseña del estudio de las calcificaciones pulmonares.

Se estudió una serie de 100 casos consecutivos de calcificaciones pulmonares y nodulares procedentes de 111 autopsias. En 71 (63.9 por ciento) de las 111 autopsias, se obtuvieron microbios parecidos al *Histoplasma capsulatum* en los focos calcificados teñidos con la técnica de metenamina-plata. Treinta y cinco de los 100 enfermos tenían además calcificaciones esplénicas y 20 por ciento de éstos revelaron microbios parecidos al *Histoplasma capsulatum*. Noventa y nueve por ciento de los sujetos estudiados vivían en la región del Meso-Sur. No pudo descubrirse ninguna correlación entre la incidencia de nódulos positivos y la ocupación del individuo.

Todas las pruebas de fijación del complemento y con colodión en la sangre obtenida en la autopsia resultaron negativas para anticuerpos contra el *H. capsulatum*. La hemaglutinación es acreedora a nuevos estudios en casos como éstos. En un caso, se descubrió un cultivo positivo para el *Histoplasma capsulatum*, pero en los otros 99 los cultivos resultaron negativos.

Resume

Calcifications pulmonaires et histoplasmose

Les auteurs fournissent une courte histoire de l'étude des calcifications pulmonaires.

Ils étudièrent une série de 100 cas consécutifs de calcifications pulmonaires et ganglionnaires de 111 autopsies. Dans 71 (63,9%) des 111 autopsies, on trouva des organismes ressemblant à *Histoplasma capsulatum* dans les foyers calcifiés, colorés par la méthode à la méthenamine à l'argent. Trente-cinq des 100 malades avaient aussi des calcifications spléniques et 20% de celles-ci révèlèrent des organismes ressemblant à *Histoplasma capsulatum*. Quatre-vingt-dix-neuf pour cent des sujets étudiés vivaient dans la région du Sud-Moyen. Aucun rapport ne put être démontré entre la fréquence de nodules positifs et l'occupation de l'individu.

Toutes les réactions de fixation du complément et les réactions au collodion, pratiquées avec le sang obtenu de l'autopsie, furent négatives pour les anti-corps contre *Histoplasma capsulatum*. Le test d'hémagglutination vaut d'être plus étudié dans des cas comme ceux-ci. Dans un cas, on trouva une culture positive pour *Histoplasma capsulatum*, mais les cultures furent négatives dans les 99 autres cas.

Acknowledgment

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TRENDS OF TUBERCULOSIS MORBIDITY AND MORTALITY[1]

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INTRODUCTION

Although tuberculosis morbidity and mortality have been decreasing for many years, the changes have not benefited all age groups of the population equally, so that now the disease affects mainly persons in the middle or older ages, particularly males.

The reason often given for the general decline is that it is due to hospitalization and treatment of tuberculous patients (1). Bloch (2) on the other hand, states that:

> We know that the lower mortality is not the mere result of the decrease in the number of new active cases, which has fallen not nearly as much as the mortality. Therefore, it must be assumed that, especially during the past 10 years of chemotherapy, the swiftness of the decline of the mortality—(is due to)—the increasing chronicity of the disease, which has shifted its weight into an older age group of the population.

However, these reasons do not explain why the tuberculosis death rate has been steadily decreasing since 1900 or earlier, so that antimicrobial drugs have merely accentuated the rate of reduction of an already decreasing mortality; nor is there any definite evidence of an increasing chronicity of tuberculosis within recent years. It is the premise of this report that the changes in tuberculosis mortality are due to similar changes in tuberculosis morbidity at various age levels, and that changes in morbidity are, in turn, to a considerable degree due to changes in environment. In presenting this thesis it is admitted that the statistical evidence for the direct relationship between morbidity and mortality is not complete and that data for the explanation of the importance of environment are even less so. This report is, therefore, not so much a presentation of new data as it is an attempt at a logical explanation of the relationships between the facts that are already known.

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TUBERCULOSIS MORTALITY

Relative changes by age: At the beginning of the present century, tuberculosis mortality was high in children less than five and reached its lowest point between five and fourteen years, after which it rapidly rose to a peak at the age of thirty, the rate for females being somewhat higher than for males. From thirty to fifty years it declined slightly, then turned upward to reach the same level at about age eighty, after which it decreased. After age thirty the rates for females were generally lower than for males. This curve is shown in table 1 and figure 1 for the year 1900.

Within the next fifty years, although all rates are lower, the distribution of mortality changed markedly. The rate for the age period from five to fourteen is still lowest, but the plateau between thirty and eighty has been eliminated, and there is a steady increase in mortality from fifteen to eighty years (table 1 and figure 1). Thus, while there has been a decrease in tuberculosis mortality at all ages, the decrease has been considerably greater in the younger groups. For example, the 1950 rate among infants was only 2.7 per cent of the 1900 rate, while among those 85 and older, it was still 23.3 per cent of the earlier rate. It is as a result of this unequal rate of decrease that the *relative* importance of tuberculosis mortality among older persons has increased, even though the rates themselves show a decline since 1900.

Relative changes by sex: In 1900 the tuberculosis death rate among males exceeded that among females by only 7 per cent. In 1950 the male rate was twice as great (table 2). Up to the age of thirty-five, at both the beginning of the century and its midpoint, there were only small differences in mortality of males and females. Among those older than thirty-five in 1900, the rate among males exceeded that among females at most by 50 per cent in some age groups, but by 1950 the divergence was so great that in some age groups the male rate was three or four times as high (table 1). In old age there is a tendency

TABLE 1

TUBERCULOSIS MORTALITY IN THE UNITED STATES, 1900 AND 1950, BY AGE AND SEX

	All Ages	Less than 1 Year	1–4 Years	5–14 Years	15–24 Years	25–34 Years	35–44 Years	45–54 Years	55–64 Years	65–74 Years	75–84 Years	85 Years and Older
1900												
Both sexes	194.4	311.6	101.8	36.2	205.7	294.3	253.6	215.6	223.0	256.1	279.3	204.5
Males	201.0	338.3	107.2	29.0	187.4	291.0	275.9	255.6	267.4	282.4	273.4	269.4
Females	187.8	284.3	96.3	43.5	222.8	297.7	229.6	174.0	179.4	231.2	284.8	157.6
1950												
Both sexes	22.5	8.5	6.3	1.8	11.3	19.1	26.1	35.9	47.4	58.2	63.2	47.7
Males	30.1	8.6	6.4	1.6	9.0	18.7	33.5	55.7	76.3	90.5	88.7	68.4
Females	15.1	8.5	6.3	2.0	13.6	19.5	18.9	16.2	18.5	28.1	41.5	33.2
1950 as a percentage of 1900												
Both sexes	11.6	2.7	6.2	5.0	5.5	6.5	10.3	16.7	21.3	22.7	22.6	23.3
Males	15.0	2.5	6.0	5.5	4.8	6.4	12.1	21.8	28.5	32.0	32.4	25.4
Females	8.0	3.0	6.5	4.6	6.1	6.6	8.2	9.3	10.3	12.2	14.6	21.1

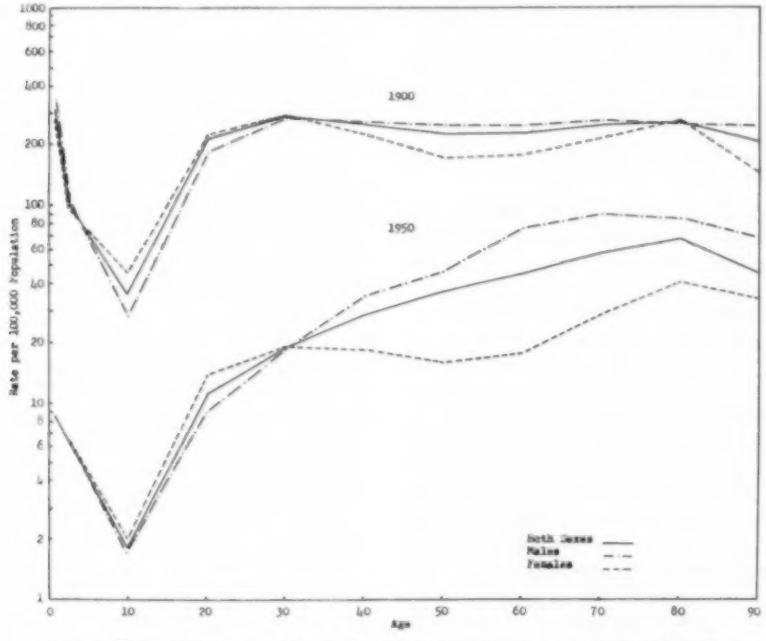

FIG. 1. Tuberculosis mortality in the United States, by age, 1900 and 1950.

for the rates to become more nearly similar for the sexes (figure 1).

Change in the pattern of mortality: Thus, within fifty years there has been a radical change in the pattern of mortality. The peak of mortality shifted from the younger to the older ages. The minor differences in mortality between males and females in 1900 increased sufficiently to relatively double the male rate. In spite of the drastic change, there are two features which remain constant. The first is that the lowest mortality is still in the five- to

fourteen-year age groups. The second is that between fifteen and thirty years the rates among females remain higher than among males (table 1 and figure 1).

Tuberculosis Morbidity

Reported cases as an index of incidence: Inasmuch as there is no accurate measure of the rate at which tuberculosis is developed in the general population, the number of new cases reported annually must be used as an index, even though there are several factors which limit its accuracy, such as variation in case-finding efforts and delays—or even failures—in reporting. Case-finding efforts may be separated into two main activities. The first, and more important, is the examination of suspects, contacts, and patients with symptoms or physical signs of pulmonary disease. This group yields most of the new cases reported annually (about 90 per cent in New York State). Case-finding efforts in this group probably do not change too much from year to year. The second activity consists of mass surveys of presumably healthy people and hospital admissions. In this group the number examined may fluctuate from year to year but, since they contribute only a small proportion of the new cases reported annually, their effect upon the trend of case reporting is not too great. Therefore, the cases reported can be used as an index of the rate of development of tuberculosis, particularly of the *trend* of incidence.

Using this indicator of incidence in comparison with death rates from 1930 to 1945, figure 2 and tables 3 and 3*A* show a marked similarity between the trends of incidence and mortality in the various age groups. The curves for incidence show the same characteristics as those for mortality, e.g.:

> The rate of decrease has been greater in the younger ages and less in the older ages.
>
> The lowest rates in both are found in the five- to fourteen-year age group.
>
> The rates are higher among females than among males less than thirty.
>
> Both cases and deaths show similar changes in each age group although the incidence lags.

This marked similarity in the rates of changes of morbidity and mortality is hardly likely to be due to chance, and is interpreted as being a cause-and-effect relationship, i.e., there were were fewer cases. The introduction of anti- fewer deaths from tuberculosis because there

TABLE 2

Tuberculosis Mortality Rates in the United States by Sex, 1900 to 1950
Ratio of Male to Female Rates, and Per Cent Change from 1900

Year	Both Sexes	Males	Females	Excess of Male Rate over Female Rate	Yearly Rate as Per Cent of 1900 (Both Sexes)
1900	194.4	201.0	187.8	7.0	100.0
1905	179.9	190.8	169.0	11.3	92.5
1910	153.8	167.1	139.8	12.0	79.1
1915	140.1	155.9	123.5	12.6	72.1
1920	113.1	116.6	109.5	10.6	58.2
1925	84.8	88.0	81.4	10.8	43.6
1930	71.1	76.2	65.9	11.6	36.6
1935	55.1	62.1	47.9	29.6	28.3
1940	45.9	54.2	37.5	44.5	23.6
1945	39.9	52.6	28.6	83.9	20.5
1950	22.5	30.1	15.1	99.3	11.6

microbial drug therapy has resulted in a steeper decline in deaths than in cases.

The tuberculin reaction as an index of morbidity: Additional evidence of lower morbidity is provided by the changes which have occurred in recent years in the proportion of tuberculin reactors in the general population. Although tuberculin-test studies are usually concerned with special groups and the figures reported are not representative of the population as a whole, there is no doubt that the proportion of tuberculin reactors has been decreasing during the past two decades or more and that this decrease has been greater among younger persons. Since tuberculous disease cannot develop in the absence of exposure, as indicated by the development of a positive tuberculin reaction, it can be assumed that the reduction in the amount of exposure is being reflected in a reduction in morbidity. That this, in turn, is reflected in mortality rates has been shown by Palmer and his associates (3) who found a high degree of correlation among naval recruits between the proportion of tuberculin reactors and tuberculosis death rates in the states from which they came.

These data suggest that, in the years prior to the introduction of antimicrobial therapy, a state of equilibrium was almost reached between cases and deaths, and that there were fewer deaths mainly because fewer cases developed each year. The introduction of drugs

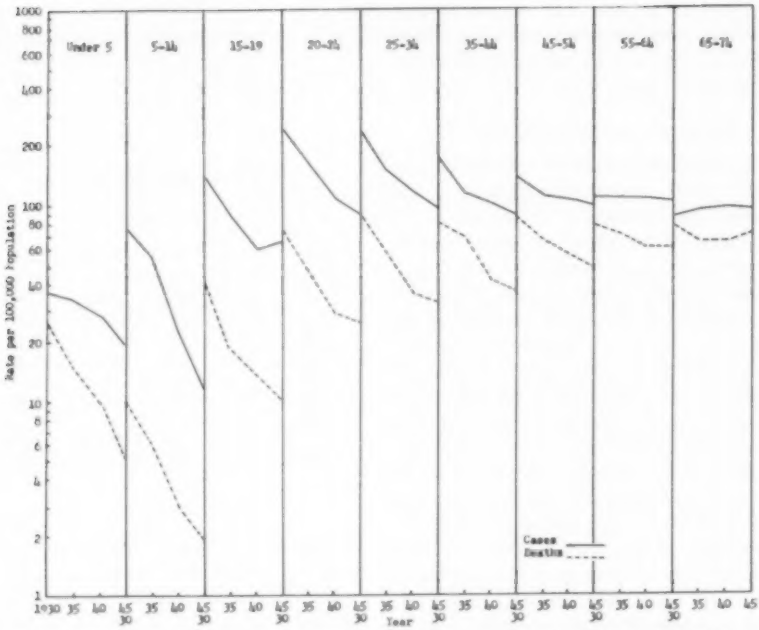

FIG. 2. Tuberculosis case and death rates, by age, upstate New York, 1930–1945.

upset this equilibrium by increasing the rate of inactivation of the disease and reducing the number of deaths. There is, however, a continuing downward trend of morbidity even after 1945, as shown in upstate New York by the steady decline in the number of new cases reported annually, as well as of the case rates. It is possible that the effect of drugs in rendering the sputum negative for *M. tuberculosis* may indirectly result in an acceleration of the rate of decrease in incidence.

Environmental factors in tuberculosis morbidity: At this point the reason is to be sought for the decreasing morbidity over the years. Variations in the rate of decrease at the various age levels may be due to environmental or constitutional factors, or both. Separation of the effects of environment and constitution upon tuberculosis morbidity and mortality in the general population is extremely difficult because of the simultaneous operation of both factors. The marked decrease in the tuberculosis morbidity during the past half century is in itself indicative of an environmental causation, since biologic changes do not usually occur within such short periods of time. It is, therefore, generally accepted that improvements in the "standard of living" are to a considerable—if not major—degree the cause of the decrease.

However, if persons of all ages could be studied under similar environmental conditions, similarity of morbidity rates at all ages would indicate more accurately the importance of environmental factors, while differences in rates would suggest constitutional causes. Such a study was made of a group of patients of all ages living in institutions of the New York State Department of Mental Hygiene under practically identical living conditions.

These patients, numbering about 100,000, were all free from tuberculosis upon admission to the institutions, as evidenced by at least one chest roentgenogram showing the lungs to be free from pulmonary disease. They were housed under essentially similar conditions regardless of age. They received chest roentgenograms on admission and periodically thereafter, all institutions having had six routine chest roentgenographic surveys, and most of them seven. Patients found with active tuberculosis were promptly segregated on tuberculosis wards. About 80 per cent of the patients were residents in mental hospitals, and 20 per cent

TABLE 3

TUBERCULOSIS REPORTED CASE RATES AND DEATH RATES BY AGE

UPSTATE NEW YORK

1930–1945

(Rates per 100,000 Population)

Age	1930		1935		1940		1945	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
years								
Total	139.6	56.0	105.4	41.7	85.4	33.7	74.4	31.7
Less than 5	37.3	24.6	33.6	15.4	26.4	9.8	19.8	5.3
5–14	74.1	9.8	55.0	6.0	23.0	2.9	11.5	1.9
15–19	140.7	39.7	87.5	18.7	59.4	13.0	63.7	10.5
20–24	243.3	71.5	156.5	45.2	106.8	28.3	89.6	25.2
25–34	235.3	89.8	153.5	54.5	117.2	35.2	92.0	32.0
35–44	161.5	78.0	128.1	66.2	99.6	40.6	86.9	35.3
45–54	140.3	81.9	117.0	62.5	104.1	53.0	97.8	46.4
55–64	114.7	74.2	112.9	69.0	113.2	59.3	100.2	58.9
65–74	(85.3	76.5	(90.6	63.6	(94.1	62.0	(93.3	69.2
75 and older	(	73.7	(	55.1	(	54.6	(	60.2

TABLE 3A

TUBERCULOSIS REPORTED CASE RATES AND DEATH RATES, BY AGE AND SEX

UPSTATE NEW YORK

1930 and 1945

Age	Males				Females			
	1930		1945		1930		1945	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
years								
Total	153.6	68.8	89.0	40.7	131.0	50.5	63.6	22.8
Less than 5	41.3	24.4	20.3	3.2	33.2	24.8	21.2	7.5
5–14	69.1	10.9	9.0	1.1	80.1	9.1	14.4	2.8
15–19	116.9	29.9	53.0	7.8	164.8	49.5	72.6	13.3
20–24	196.0	53.0	65.5	20.7	289.9	89.8	114.0	29.5
25–34	235.5	90.9	83.4	27.2	235.1	88.7	110.2	36.5
35–44	196.1	100.0	109.3	45.5	125.4	55.1	75.5	25.3
45–54	196.2	118.6	146.8	70.2	82.5	43.9	51.2	22.1
55–64	160.8	103.3	158.1	95.0	69.3	45.2	46.1	22.6
65 and older	110.4	90.9	149.2	98.3	62.9	61.9	55.8	38.8

were inmates of schools for the mentally retarded.

The incidence rates among the adult patients are shown in figure 3 and table 4, using the interval between the first and second surveys (late 1941–1946) as the starting point. It may be seen that, even though there was some variation in the level of incidence at the beginning and end of the study period, in general there has been a decrease in incidence at all ages and the rate of decrease is roughly similar for all ages, the curves being parallel to each other, as opposed to the changes in case rates for upstate New York, in which the decrease in morbidity is much less for the older ages.

This difference between the general population and hospitalized mental patients in the trend of

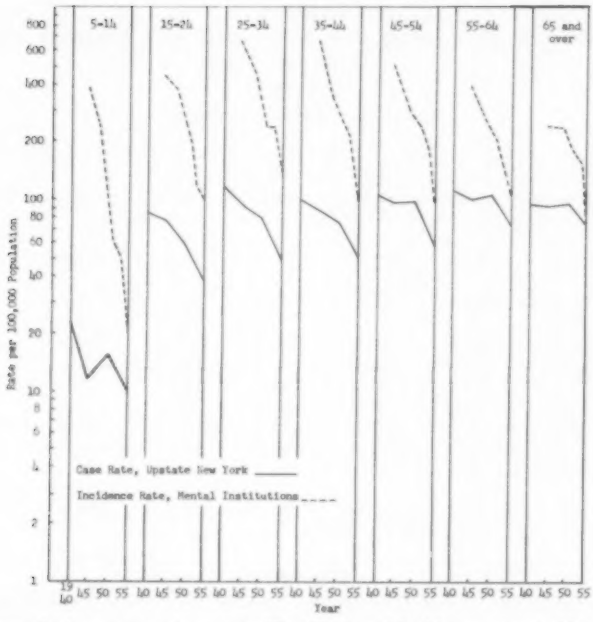

FIG. 3. Tuberculosis case rates in upstate New York and incidence rates in New York State mental institutions, by age.

TABLE 4

INCIDENCE OF PULMONARY TUBERCULOSIS AMONG PATIENTS IN MENTAL HYGIENE INSTITUTIONS
NEW CASES AND RATES PER 100,000 PERSON-YEARS

Age and Sex	Period Between									
	1st and 2nd surveys		2nd and 3rd surveys		3rd and 4th surveys		4th and 5th surveys		5th and 6th surveys	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
years										
All patients Total*	1,582	487.4	955	306.7	518	208.2	321	173.2	228	100.4
Less than 5	4	1,030.9	4	646.2	—	—	1	108.2	—	—
5-14	35	377.7	25	205.4	7	57.7	4	46.1	2	21.9
15-24	124	429.7	104	365.4	38	175.0	19	123.3	15	95.1
25-34	294	670.4	180	448.4	68	228.9	50	225.1	34	131.2
35-44	402	678.8	181	331.8	101	248.0	62	207.4	36	99.0
45-54	328	507.4	175	301.8	104	228.1	66	194.5	44	103.9
55-64	230	397.0	140	250.7	88	198.3	47	140.7	47	113.9
65-74	123	329.7	104	280.0	75	238.5	45	188.8	24	75.8
75 and older	38	187.4	36	158.1	27	194.9	21	123.4	25	106.2
Males—total	981	642.6	598	413.0	331	284.3	202	233.7	127	119.5
Females—total	601	349.6	357	214.3	187	141.3	119	120.4	91	75.3

* Includes age not stated

tuberculosis morbidity at various age levels is interpreted as being due to differences in environment. In mental institutions, patients of each sex live under quite similar environmental conditions, with similar opportunities for exposure to infectious tuberculosis and, therefore, may be expected to be affected equally by environmental changes. When these changes are produced by a tuberculosis control program with its emphasis upon early diagnosis and early segregation of active cases, patients of all ages benefit from the reduction of exposure, and the rate of decrease in morbidity is similar for all.

For the general population, however, improvements in environment probably do not affect all age groups equally. For children younger than five years, in addition to the general reduction in environmental exposure, there is the benefit derived from pasteurization of milk. Since the disease in this age group is mainly acquired as a result of exposure within the confines of the household, the decrease in tuberculosis among these children depends upon the general downward trend of tuberculosis morbidity to reduce the number of infectious households. The group between five and fifteen not only has the advantage of a constitutionally high level of resistance, as will be considered below, but also has benefited from environmental improvements because, as standards of living improve, parents are prone to provide their children with physical comforts before accepting them for themselves. For those between twenty and forty-five, the decrease is probably related to improved working conditions, housing, better nutrition, et cetera. Those more than sixty-five show relatively little reduction in tuberculosis morbidity, probably because they have not benefited to the same degree from improvements in environment.

Constitutional factors in tuberculosis morbidity: The radical changes which have occurred within the past half century indicate that environmental factors play a major role in determining trends of tuberculosis morbidity and mortality, since constitutional changes of such magnitude are hardly to be expected in such a relatively short period of time. However, that physiologic factors do play some part is indicated by the fact that all statistical reports show the lowest incidence and mortality in the five- to fourteen-year age group and that, between fifteen and thirty, females show somewhat higher rates than males. These phenomena are universally present regardless of the level of the curves of morbidity and mortality. Also, they were present even during the period when infection rates, as indicated by positive tuberculin reactions, were much higher than they are at present. They were also present among the mental patients in this study, in spite of the similar environmental conditions for patients of all ages and both sexes.

From the data presented, therefore, it appears that there are two factors concerned with the decrease in tuberculosis morbidity and mortality. The general reductions are probably due to improvement in environmental conditions, unequally affecting different segments of the population; but the effects are modified by age-specific factors in early childhood and in young women.

The consistently lower incidence of tuberculosis among women more than thirty than among men of similar age is probably due to more pronounced improvements in environmental conditions for females. For example, while working conditions during the past fifty years have improved for both sexes, legal regulation of working conditions for women is stricter than for men. Certainly, the burden of housework has been greatly lessened during the past half century. The lower incidence rates among females than among males in mental hospitals is probably due to differences in exposure of the sexes to infectious tuberculosis. Patients with unrecognized tuberculosis or with the disease in a latent stage on admission act as foci of infection among patients of both sexes within the institutions. Since the prevalence of tuberculosis upon admission is about twice as high among men, it might be reasonable to expect more of these cases among males, with correspondingly greater opportunities for infection. It is important to note in this connection that it was found, in a previous study (4), that survival rates among women are the same as among men in the same stage of disease, indicating similar degrees of resistance.

The medical literature is replete with warnings regarding the hazard to the young of exposure to tuberculosis. Since the data from the mental institutions show that the old are as apt to develop tuberculosis as the young (*see* table 4 and figure 3), recommendations regarding the need to reduce exposure to infectious tuber-

culosis must be revised to include all age groups. Warnings against the hazards of exposure must, therefore, be extended to *all* contacts of infectious cases, regardless of age.

Discussion

Considerable emphasis is placed in the tuberculosis literature upon the fact that the curve of tuberculosis case rates does not run parallel with that for death rates, and did not even before the development of antimicrobial therapy. Edwards and Drolet (6) call this the "widening gap" between morbidity and mortality, and Drolet and Lowell (1) conclude from it that "it is mortality which is declining rather than morbidity." There are several factors which may explain, at least in part, the divergence of the curves:

> The conduct of mass surveys since about 1940 tends to keep the case rate up, even though these surveys contribute a small proportion of the total of new cases reported annually.
>
> Even in the absence of drug therapy, the increasing availability during the past twenty years of hospital facilities for the tuberculous has kept alive some patients who would have died without hospitalization.
>
> Improved standards of living may of themselves keep some patients alive who would previously have died. There are persons who are heavily exposed to infectious tuberculosis, but who develop less extensive disease because of better nutrition, housing, and other environmental conditions.

As a result of these considerations, it is believed that the lack of parallel between the morbidity and mortality curves does not seriously affect the explanation of the direct causal relationship between morbidity and mortality.

The tendency of the incidence of tuberculosis to become more nearly similar for all ages when environmental conditions become uniform is an indication that the native resistance of man to tubercle bacilli does not differ with age as much as is sometimes thought. Basically, human resistance to tuberculosis is quite high. For example, at the beginning of the century, even though almost 100 per cent of adults were tuberculin positive, thereby showing evidence of significant exposure to infectious tuberculosis, deaths from this disease represented only 2 per 1,000 population, or 0.2 per cent. Also, in the Lübeck episode, in which human infants were fed virulent tubercle bacilli by mouth, only 28.7 per cent died, indicating a relatively high level of resistance even among newborn infants (5). Clinical evidence of man's inherent resistance is presented by the results of mass chest roentgenographic surveys. Reports of these surveys show more persons with inactive tuberculosis than with active disease. These persons have never been reported as cases of tuberculosis nor have they received treatment for this disease. The most logical explanation of this is that they had, unknowingly, developed active tuberculosis in the past, which they were able to control without any change in their mode of living.

The relatively high mortality, even at present, among children less than two or three years of age is often cited as evidence of their lack of native resistance to tuberculosis. This may be true, but care must be used in the comparison of tuberculosis mortality and morbidity rates among infants with those of adults, because of differences in conditions of exposure. The infant, because of his immobility, must obtain his tuberculous infection from members of his own household. Because of his helplessness, he is in most intimate contact with members of the family and for practically twenty-four hours per day. As a result, he is exposed to closer, more continuous infection than other members of the family. Since resistance to tuberculosis is, at best, a relative thing, it is not surprising that the disease occurs in infancy as frequently as it does. Furthermore, the fact that the reduction in mortality was greater among those less than five years of age than in any other age group (figure 1) is an indication that other factors than native resistance are involved, such as the introduction of pasteurized milk and the reduction in the number of households whose members have infectious sputum.

The high degree of resistance in the five- to fourteen-year group is probably the result of physiologic factors, as indicated above.

The much greater decrease in morbidity and mortality among women more than thirty years old than among men suggests that the environmental improvements of the past half century, rather than an increasing resistance, have benefited females more than males, since it is difficult to conceive of constitutional changes occurring during this time sufficient in degree to account for the greater decrease.

The assessment of the importance of constitutional and environmental factors in the older

portion of the population is quite difficult. As age increases, the burden of physical infirmities other than tuberculosis increases rapidly, so that the actual cause of death becomes difficult to determine. Therefore, tuberculosis mortality statistics showing high death rates in the aged must be accepted with some reservations. That tuberculosis in the aged can be—and probably is—usually newly developed rather than the reactivation of a long-dormant infection is shown by the rates of newly acquired disease in table 4. The data also indicate that the aged have shown least improvement in the tuberculosis picture. This is probably due to their inability to effect improvements in environmental conditions such as housing, nutrition, and working conditions.

Summary

Within the past fifty years there has been a marked change in the pattern of tuberculosis mortality, and the peak of mortality has shifted from the younger to the older age groups. During the same period there has also been a similar change in morbidity. This marked similarity in the rates of change of morbidity and mortality is interpreted as evidence of a cause-and-effect relationship, i.e., even before the advent of chemotherapy there were fewer deaths from tuberculosis because there were fewer cases. Most of the improvement is due to environmental factors, but the effects of environment are modified by age-specific factors in early childhood and in young women. The data presented indicate that, under similar conditions of environment and exposure, the disease tends to attack all ages equally.

Sumario

Tendencias de la Morbidad y la Mortalidad en la Tuberculosis

Durante los últimos cincuenta años ha habido una notable alteración en el patrón de la mortalidad tuberculosa, y la cúspide de la mortalidad se ha desviado de los grupos más jóvenes a los de mayor edad. Durante el mismo período de tiempo ha tenido lugar un cambio semejante en la morbidad. Esa notable semejanza en las tasas de alteración de la morbidad y la mortalidad se interpreta como prueba de una relación de causa y efecto; es decir que, aun antes del advenimiento de la quimioterapia, había menos fallecimientos de tuberculosis porque había menos casos. La mayor parte del adelanto se debe a factores del ambiente, pero los efectos del ambiente son modificados por factores específicos para la edad a principios de la niñez y en las mujeres jóvenes. Los datos expuestos indican que, en condiciones semejantes de ambiente y exposición, la enfermedad tiende a atacar por igual a todas las edades.

Resume

Tendances de la morbidité et de la mortalité tuberculeuses

Au cours des ces cinquante dernières années, il y a eu un changement net dans le mode de mortalité tuberculeuse, et le maximum de mortalité a changé des groupes jeunes aux groupes plus agés. Pendant la même période de temps il y eut un changement semblable dans la morbidité. Cette ressemblance nette dans les taux de changements de morbidité et de mortalité est interprétée comme l'évidence d'une relation de cause à effet, c'est à dire que, même avant l'avènement de la chimiothérapie, il y avait peu de morts par tuberculose parce qu'il y avait moins de cas. Cette amélioration est due, pour la plus grande part, à des facteurs de milieu dans la prime enfance et chez les jeunes femmes, mais les effets du milieu sont modifiés par des facteurs spécifiques de l'âge. Les données rapportées indiquent que, dans des conditions semblables de milieu, et de contact, la maladie tend à attaquer également tous les âges.

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THE EFFECT OF DIETARY FAT AND VITAMIN A ON AVIAN TUBERCULOSIS IN CHICKS[1, 2]

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INTRODUCTION

Meaningful studies regarding the influence of nutritional factors upon pathologic processes in experimental disease require that the state of a specific host be easily defined in nutritional and biochemical terms. In a previous publication (1) it was suggested that the chick might be a desirable host and that avian tuberculosis is a disease readily manipulated and easily studied. Pure genetic lines of chicks are available, and their nutritional requirements are defined. *Mycobacterium tuberculosis*, avian strain, produces a chronic, fatal disease which follows a predictable course and is characterized by tubercles whose development essentially parallels that observed in man.

The literature concerning the interactions of nutrition and infection has been reviewed by Clausen (2) and Scrimshaw and associates (3). The latter emphasize that definite patterns of interactions can be recognized. Factors which may favor progress of disease include age, vitamin deficiencies, protein or amino acid deficiencies, and nutrients in excess of host requirements. As opposed to factors enhancing infections, certain deficiencies may retard progress of infection.

The relationship of nutrition to infection has been investigated more intensively in tuberculosis than in other infectious diseases. The effects of protein, vitamin A, D, and those of the B complex, minerals, and fats have been studied (4). Special importance has been attributed to the role of fat in the case of tuberculosis. The earlier studies have been summarized by Hedgecock (5).

Hedgecock (5) has reported that the absence of fat from a diet adequate in protein increases resistance of mice to experimental tuberculosis as compared with resistance of mice fed diets containing unsaturated fats. In a study involving in part the role of fat, Dubos (6) showed that, when mice were fed a diet very low in fat, resistance to tuberculosis was not decreased when adequate protein was supplied in the diet. The reduction of dietary protein to 5 per cent without the addition of fat decreased the resistance to infection. The higher level of resistance to tuberculosis was restored if the low protein diet was supplemented with 20 per cent fat administered as peanut oil. Thus, there appears to be an interaction between levels of dietary fat and protein in the resistance of mice to tuberculosis. Hedgecock (7) has also noted the limited interchangeability of fat and protein concentrations with regard to their effects on resistance.

The importance of the composition of fat was indicated by Hedgecock (5) demonstrating an increase in resistance of mice to tuberculosis when the major portion of a 20 per cent dietary fat level was supplied by fat containing a high proportion of saturated fatty acids as compared with unsaturated fatty acids. He associated high levels of oleic acid with increased susceptibilty to tuberculosis. In a subsequent study, Hedgecock (7) found that a mixture of three parts saturated to one part of unsaturated fatty acids at a 5 per cent dietary level, with 20 per cent casein in the diet, offered the greatest protection against experimental tuberculosis in mice, as compared with the same amount of fatty acid in diets containing lower or higher concentrations of casein. The severity of the infecting challenge was a significant factor in demonstrating the effects of diet (7). The relationship of severity of infecting challenge to demonstration of dietary effects has been noted by others (8–10).

The effect of vitamin A on tuberculosis has been studied with the mouse, rabbit, and guinea pig as test animals. The results have been discordant. In a single report on the mouse, vitamin A deficiency accelerated progress of the disease

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(11) but, in the guinea pig and rabbit, vitamin A deficiency did not influence the course of the disease (12–14).

The present report describes the effects of various concentrations of fat and of vitamin A in the diet on the progress of avian tuberculosis in the immature domestic fowl under different challenge dosages. In studying the pathogenesis, changes in growth curve, median survival time, tissue reactions, and alterations in serum electrophoresis patterns have been investigated. The serum studies are discussed in detail in a separate report, but a summary is included here.

Materials and Methods

Inoculum: The infecting organism was *M. tuberculosis*, avian strain Kirchberg. The strain has been maintained by serial transfer in Tween®-albumin medium. It has shown constant virulence for chicks over a period of five years. A standard suspension was prepared by diluting 12- to 14-day-old Tween-albumin cultures to a turbidity permitting 40 to 45 per cent transmission of light at 600 mμ.[3] Suspensions for infecting animals were then prepared by dilution of the standardized suspensions with Tween-albumin medium. Test animals were injected intravenously into the left jugular vein with 0.5-ml. amounts of suspension.

Animals: Day-old white leghorn cockerels were used in all trials except the first when a Columbian x New Hampshire cross was used. The chicks were banded and distributed at random among the various experimental groups. The animals were placed on their designated diets at two days of age.

Dietary regimens: The basal diet consisted of:

	Per cent
Soybean oil meal	30.0
Fish meal (Menhaden)	2.5
Ground whole wheat	63.4
Methionine	0.1
Ground limestone	1.5
Dicalcium phosphate	1.5
Salt (iodized)	1.0
	Gm. per 100 lbs. of feed
Trace minerals	113.4
Manganese sulfate	11.5
BY-24 (riboflavin)	3.9
Vitamin D (3,000 ICU[4]/mg.)	3.5
	Mg. per 100 lbs. of feed
Vitamin A (371,000 IU[5]/gm.)	329

This mixture contained 24 per cent protein and 1.5 per cent fat and was, by calculation, nutritionally adequate in all other dietary factors. In these studies no attempt was made to make the diets isonitrogenous. The various fat levels were obtained by substituting (by weight) corn oil or coconut oil for whole ground wheat. The oils were fully refined, deodorized, and bleached. The fatty acid analyses of corn and coconut oils are as follows:

Corn Oil (unsaturated)				Coconut Oil (saturated)			
Saturated Fatty Acid		Unsaturated Fatty Acid		Saturated Fatty Acid		Unsaturated Fatty Acid	
per cent		*per cent*		*per cent*		*per cent*	
Palmitic	7.4	Oleic	46.0	Caproic	0.2	Oleic	6.0
Stearic	3.5	Linoleic	42.3	Caprylic	8.0	Linoleic	2.5
Arachidic	0.6		88.3	Capric	7.0		8.5
Lignoceric	0.2			Lauric	48.2		
	11.7			Myristic	17.3		
				Palmitic	8.8		
				Stearic	2.0		
					91.5		

For the vitamin A studies, corn oil was added to a concentration of 6 per cent by weight, yielding a total fat concentration of 7.5 per cent. The amounts of vitamin A were altered to yield a concentration of 1,000 or 2,000 IU per pound of diet.

Housing: The chicks were maintained in a brooder having an initial hover temperature of 95 to 100° F. which was reduced steadily until the chicks were four to five weeks of age, and thereafter were kept in a growing battery at room temperature. Diurnal room temperature varied between 60° and 75° F.

Biologic sampling and related methods: Feed consumption was recorded daily and body weights weekly. Blood and tissue samples were obtained from animals sacrificed four to five weeks after infection. Serum was separated from all blood samples, frozen within five hours from sampling, and stored in this state until the time of analysis. Body, liver, and spleen weights were recorded, and samples of liver and spleen, lung, kidney, heart, pancreas, testis, adrenal, and femoral bone were preserved in Bouin's solution and/or 10 per cent formalin.

Histologic methods: Details regarding the procedure for histologic study and evaluation will be given elsewhere (15). Following intravenous inoculation of avian tubercle bacilli, tubercles were found predominantly in the liver and spleen. The character and extent of the tissue reaction were estimated according to the following criteria: (*a*) number of tubercles per low power field; (*b*) developmental stage of the tubercles; there are six stages ranging from small collections of epithelioid cells to the mature tubercle; (*c*) leukocytic reaction ranging from one to four plus; in this category are included lymphocytes, other lymphoid cells, and granulocytes; (*d*) amyloid deposition in the tubercle ranging from one to four plus.

[3] With a Bausch and Lomb Spectrophotometer "Spectronic 20."

[4] International Chick Units.

[5] International Units.

Procedure and Results

Effect of variations in dietary fat level: The dietary fat levels used were 1.5 per cent for low fat, which was the concentration present in the basal diet; 9.5 per cent for medium fat (8 per cent added); and 17.5 per cent for the high-level fat (16 per cent added).

Trial I: In the first trial the chicks were allocated to each of six test groups of 25. There were three groups of infected animals receiving, respectively, low, medium, and high levels of fat, and three groups of uninfected controls receiving the corresponding diets. The added fat was in the form of corn oil.

The alterations in dietary fat level from the medium level (normal) did not produce significant changes in the growth curves in spite of the fact that the rations were not isonitrogenous. The growth curves of such uninfected animals are shown in figure 1. A similar lack of effect was observed in all other experiments with the same dietary fat levels.

At 12 days of age, chicks weighed 90 to 95 gm. and were infected with a 1:10 dilution of the standardized suspension of culture. When the growth curves for the infected chicks showed a significant rate decline, one-half of the birds of each group was sacrificed and samples of tissue were obtained for biochemical and pathologic studies.

This decline in growth rate, which occurred 35 days after infection, was accompanied by a depression in feed utilization, a phenomenon which will be reported elsewhere as being as sensitive as weight change for determining progress of the disease syndrome. Previous studies indicated that deaths could be expected following significant decrease in the growth curves. The remaining groups, designated for determination of median survival time, were maintained for a total of 70 days after infection. At this time, only one bird, which was in the low-fat group, was alive among the infected chicks. None of the uninfected birds died during the trial.

The median survival times for this trial as well as for all subsequent trials are summarized in table 1. The median survival time for the low-fat group was 53.3 days as compared with 50.7 days for the medium-fat group, and 46.7 days for the high-fat group.

Trial II: Test groups of 20 chicks each were used. Three groups of infected animals received, respectively, low, medium, and high levels of fat. Three groups of uninfected controls received the corresponding diets. The infecting inoculum was of the same concentration as that used in the first trial, a 1:10 dilution of standardized suspension. In this trial, and in all subsequent experiments, the chicks were one week old and weighed 70 to 75 gm. at the time of infection.

A significant difference in the growth curve of infected versus noninfected birds was observed at 31 days following inoculation. The animals designated for serum and tissue study were bled and sacrificed on the thirty-second day, and the experiment terminated on the seventieth day after inoculation. At this time, among the infected birds, there was one survivor in the low-fat group, 2 in the medium-fat group, and none in the high-fat group. All uninfected birds were alive at this time.

As may be seen from table 1, the median survival time was 54.4 days for the low-fat group, 48.6 days for the medium-fat group, and 42.6 days for the high-fat group.

Trial III: In the third trial, the procedure was altered with regard to the infecting dose. Furthermore, the study of dietary components was extended to include coconut oil (a saturated fat) for comparison with corn oil (an unsaturated fat). The test groups are tabulated below:

	Number of Chicks				
	Level of Fat in Diet				
	Low	Medium		High	
	—	Corn Oil	Coconut Oil	Corn Oil	Coconut Oil
Not infected	20	20	20	20	20
Infected	20	20	20	20	20

A significant change in the infecting inoculum was introduced in this trial by use of an undiluted standardized suspension instead of the tenfold dilution.

Depression of the growth curves was observed on the twenty-eighth day after infection, and the animals designated for serum and tissue study were then bled and sacrificed to obtain tissue samples. The trial was terminated at 72 days after inoculation, with a 100 per cent mortality in the infected groups. One death occurred at 60 days of age, for reasons unknown, in the

uninfected animals fed the medium fat-corn oil diet.

The data in table 1 show that the median survival time for the infected animals on the corn oil series was 42.2 days for the medium-fat level and 46.8 days for the high-fat level. The corresponding values for the coconut oil groups were 44.7 and 45.1 days. The low-fat level gave a median survival time of 50.8 days.

Trial IV: The results obtained in *Trial III*, in which undiluted inoculum was used, were studied further. This trial was designed to compare the effects of two levels of infecting inoculum, undiluted and diluted, 1:10, at the three dietary fat levels. Thirty chicks were allocated to each test group. At each of the levels of challenge, including uninfected controls, three groups received, respectively, the low, medium, and high levels of dietary fat.

The added fat in the trial was corn oil. The animals assigned to the tissue and serum study were bled and sacrificed 34 days after infection, and the experiment was terminated 72 days after infection.

At this time, among the infected groups there were, in the diluted inoculum series, two survivors in the low-fat group, one in the medium-fat group, and none in the high-fat group. There were no survivors in the undiluted inoculum groups. Among the uninfected animals, one death occurred for unknown reasons at the high-fat level on the sixty-second day of age.

As may be seen in table 1, the median survival time for animals challenged with the dilute infecting inoculum was 52.9 days at the low-fat level, 50.9 days at the medium-fat level, and 50.5 days at the high-fat level. The respective values for animals challenged with the high infecting inoculum were 42.0 days, 46.6 days, and 43.8 days.

TABLE 1

MEDIAN SURVIVAL TIME (DAYS) OF CHICKS INFECTED INTRAVENOUSLY WITH AVIAN TUBERCLE BACILLI AND FED VARIOUS LEVELS OF DIETARY FAT

Infecting inoculum: Standardized suspension diluted 1:10

Trial Number	Level of Corn Oil in Diet		
	Low	Medium	High
I	53.3	50.7	46.7
II	54.4	48.6	42.6
IV	52.9	50.9	50.5
Mean ± S.E.	53.5 ± 0.4	50.1 ± 0.6	46.6 ± 1.9

Infecting inoculum: Standardized suspension undiluted

Trial Number	Low Fat (none added)	Medium Fat		High Fat	
		Corn Oil	Coconut Oil	Corn Oil	Coconut Oil
III	50.8	42.2	44.7	46.8	45.1
IV	42.0	46.6	—	43.8	—
Mean ± S.E.	46.4 ± 3.1	44.4 ± 1.6	—	45.3 ± 1.1	—

Tissue Reactions

The estimations of tissue changes are summarized in tables 2 and 3. In *Trials III* and *IV*, increasing the dietary fat level resulted in an increase in the number of tubercles in the spleen when the diluted inoculum was used. This effect of dietary fat was not apparent when the test animals were challenged with undiluted inoculum.

Birds receiving coconut oil in the diet demonstrated a greater number of tubercles in the liver than those that received corn oil. This effect was aggravated by raising the level of the coconut oil in the diet. A slight increase in the amount of amyloid deposits in the tubercles resulted when the corn oil level was increased, but was not evident with coconut oil in the diet.

Biochemical Changes in Blood Serum Components

Alterations of serum proteins, lipoproteins, and their constituent fractions induced by infection as related to dietary fat content were investigated by paper electrophoresis. In *Trials III* and *IV*, infection caused significant decrease in albumin from 45 to 5 per cent of total protein; increases in alpha-3-globulin from 14 to 22 per cent; in beta-globulin from 10 to 19 per cent; and in gamma-globulin from 14 to 38 per cent. As a result, the albumin/globulin ratio was inverted from 0.85 to 0.06.

Serum protein was significantly increased. These changes were not influenced in magnitude or direction by dietary fat level. The results of *Trial III* demonstrated that the degree of unsaturation of the dietary fat was also without effect on the serum protein changes.

Equally marked alterations in the distribution of protein-bound lipids were found as a result of infection. Two major lipoprotein fractions

TABLE 2

EFFECT OF DIETARY FAT (CORN OIL) LEVELS ON TISSUE REACTIONS OF CHICKS INFECTED WITH M. TUBERCULOSIS, AVIAN KIRCHBERG STRAIN (TRIAL IV)

Level of Infection	Level of Dietary Fat	Body Weight at Sacrifice	Liver					Spleen			
			Weight	Number of Tubercles/ LPF*	Stage of Tuberculosis	Leukocytic Reaction	Amyloid	Weight	Number of Tubercles/ LPF*	Stage of Tuberculosis	Amyloid
		gm.	*gm.*					*per cent*			
Not infected	Low	517	15.2	—	—	—	—	1.6	—	—	—
	Medium	559	14.8	—	—	—	—	1.4	—	—	—
	High	490	15.0	—	—	—	—	1.3	—	—	—
Medium	Low	442	31.2	27	2.7	1.5	0.5	2.8	9	2.1	0.0
	Medium	463	29.0	27	2.6	1.7	0.9	2.7	12	1.9	0.0
	High	443	30.1	29	2.7	0.9	1.5	2.8	16	2.5	0.8
High	Low	339	34.9	62	2.8	1.4	0.0	2.8	27	2.5	0.0
	Medium	348	36.8	62	2.5	1.0	0.2	2.9	28	2.4	0.0
	High	391	41.1	54	2.7	1.5	0.3	3.3	27	2.7	0.1

*Low power field

TABLE 3

EFFECT OF TYPE AND LEVEL OF DIETARY FAT ON TISSUE REACTIONS IN CHICKS INFECTED WITH M. TUBERCULOSIS, AVIAN KIRCHBERG STRAIN (TRIAL III)

Level of Infection	Level of Dietary Fat	Type of Fat	Body Weight	Liver					Spleen			
				Weight	Number of Tubercles/ LPF*	Stage of Tuberculosis	Leukocytic Reaction	Amyloid	Weight	Number of Tubercles/ LPF*	Stage of Tuberculosis	Amyloid
			gm.	*gm.*					*gm.*			
Not infected	Low	—	441	11.6	—	—	—	—	1.0	—	—	—
	Medium	Corn	425	11.4	—	—	—	—	1.2	—	—	—
	Medium	Coconut	405	11.6	—	—	—	—	0.9	—	—	—
	High	Corn	393	10.9	—	—	—	—	1.0	—	—	—
	High	Coconut	382	10.6	—	—	—	—	0.8	—	—	—
Medium	Low	—	369	28.0	44	2.3	1.3	0.8	2.6	25	2.0	0.2
	Medium	Corn	395	23.2	45	2.5	0.8	0.1	2.3	28	2.5	0.2
	Medium	Coconut	359	23.1	52	2.1	0.7	0.6	2.6	21	2.4	0.3
	High	Corn	362	21.8	39	2.5	1.6	0.4	2.6	28	2.6	0.2
	High	Coconut	301	21.4	61	2.8	0.4	0.6	2.1	28	2.8	0.3

*Low power field

were separable, viz., an alpha fraction associated with the alpha-globulins and a beta fraction associated with mobility of beta and gamma globulins. Infection caused inversion of the beta/alpha lipoprotein ratio from 0.43 to 2.00, resulting from changes in both fractions. The rise in beta lipoprotein accompanied the increases of beta and gamma globulins noted above. However, alpha-3-globulin increased while lipid bound to that fraction decreased. This may indicate synthesis of an atypical protein in response to infectious processes. Dietary fat level and degree of unsaturation were not only without influence on these changes, but also failed to correlate with serum levels of total protein-bound lipid.

The Effect of Variations in Vitamin A Level

Two levels of vitamin A, 1,000 and 2,000 IU per pound of feed, were tested with three levels

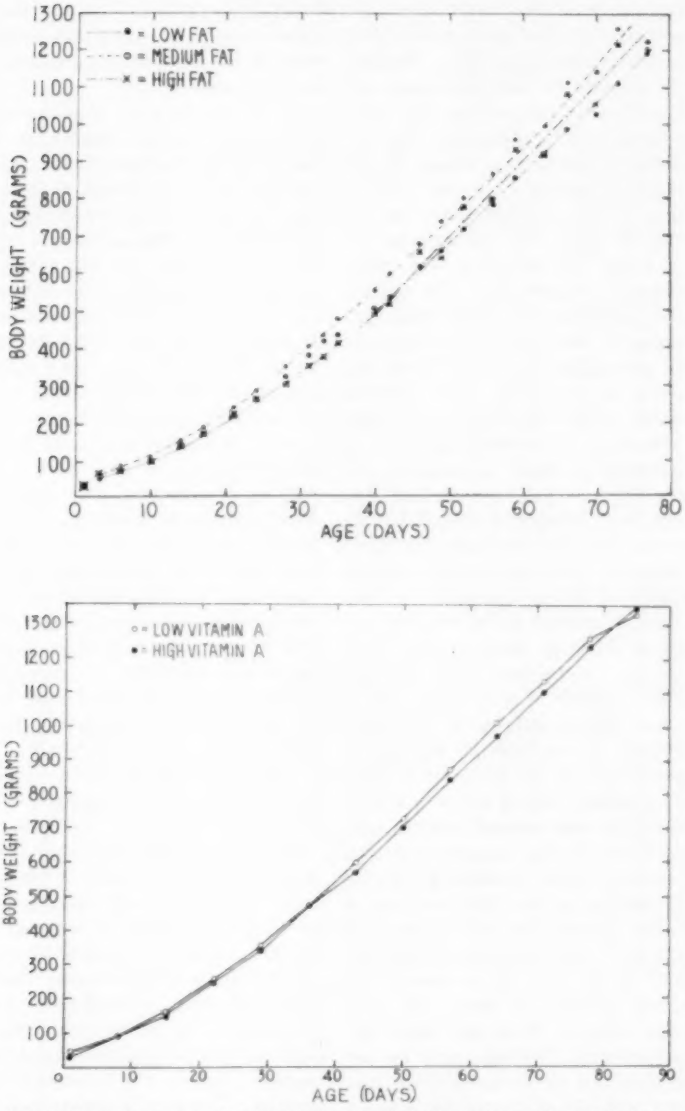

FIG. 1. Growth curves of uninfected control chicks fed experimental diets.
Fat
Vitamin A

of infecting inoculum. As shown in figure 1, the differences in the levels of vitamin A did not affect the growth curves of uninfected chicks. The average weight per bird for the two groups at each of eight successive weeks did not differ by more than 5 per cent, and at the end of eight weeks the birds fed the 1,000 IU vitamin A diet weighed an average of 880 gm. as compared with 850 gm. for the groups fed the 2,000 IU vitamin A. The high level of infecting inoculum was undiluted suspension permitting 40 per cent transmission of light at 550 mμ. The me-

dium level was a 1:10 dilution of the standardized suspension, and the low level was a 1:50 dilution of the standardized suspension. Twenty-five birds were assigned to each test group; 10 of these were sacrificed at thirty-nine days after infection for assessment of pathologic involvement. At this time, a decline was evident in the rate of weight gain of chicks on the low level of vitamin A infected with the high inoculum as compared with the uninfected controls at the low vitamin A level. The remaining birds were held for assessment of mortality. The experiment was ended eighty-four days after challenge.

An examination of data, both on median survival time and percentage survival at the end of the test period, is pertinent. The survival curves are shown in figure 2. At the high level of infecting inoculum, the increased amount of vitamin A produced a small prolongation of survival time. The median survival time for chicks fed "adequate" vitamin A was 51.5 days as compared with 48.5 days for those on "low" vitamin A, and one animal in each test group was alive at the end of the test period. In examining the data for animals at the medium and the low levels of infecting inoculum, per cent survival at the end of the test period was the more instructive statistic. Under these conditions, there were significantly more survivors among the animals on the 2,000 IU vitamin A diet than among those on the 1,000 IU vitamin A diet. At the medium level of infecting inoculum the estimated median survival time for adequate vitamin A was 59 days as compared with 56 days for animals on low vitamin A, and 20 per cent of the animals on the adequate vitamin A were still alive as compared with 7 per cent on low vitamin A. At the low level of challenging inoculum (1:50 dilution), 27 per cent of the animals on "low" vitamin A were still alive, whereas 53 per cent of those on "adequate" vitamin A had survived. The differential for per cent survival increased as the severity of challenge decreased; 13 per cent with the medium inoculum and 26 per cent with the low inoculum.

Discussion

This report is one of a series of continuing studies on the relationship of dietary components to the pathogenesis of tuberculosis in chicks. The test system would appear advantageous in being related to a naturally occurring infection in the test host, and the experimental infection appears sufficiently prolonged to allow time for interaction of nutritional changes and host response.

A consideration of experimental procedures in the present study shows that the amount of the infecting inoculum was a critical factor in demonstrating the effects of dietary factors. In the two trials in which an undiluted standardized suspension of organisms was used, characterized by a median survival time of 44 days for the group on a medium fat dietary level, alterations in the fat concentration in the diet did not produce a consistent effect on progress of the disease. When the inoculum was diluted tenfold, giving a median survival time of approximately 50 days for the medium fat level group, feeding fat at a low concentration in diet led to an increased median survival time and a decreased number of tubercles. The observed differences were small, but a trend was evident across three levels of fat in the diet. These results suggested that more slowly progressive infection might be more useful in revealing effects of nutrition on the progress of disease. In view of the extended time required for each experiment, as balanced against the desirability for surveying other components of diet, the use of more slowly progressing infection was applied to the next factor selected for study, vitamin A.

The study with vitamin A revealed that under conditions in which prolonged survival was attained, the effect of a nutritional factor could be demonstrated more effectively than with an infecting inoculum leading to the death of all or nearly all experimental animals. With the lowest of the three inoculi of organisms, the experimental conditions approached natural ecologic conditions, in which disease does not lead to death of nearly all members of a population. This result is in accord with Schneider's position that survivorship is more significant than mean survival time in the assessment of the role of nutritional factors. A similar inverse relationship of infecting inoculum to response to diet factors also has been observed by Hedgecock. The increased survival time observed with decreasing dietary fat level is in general accord with Hedgecock's studies on the effect of diet fat on tuberculosis in mice, but the differences obtained with chicks are much smaller than those observed by Hedgecock for mice. A smaller infecting inoculum might bring the magnitude of re-

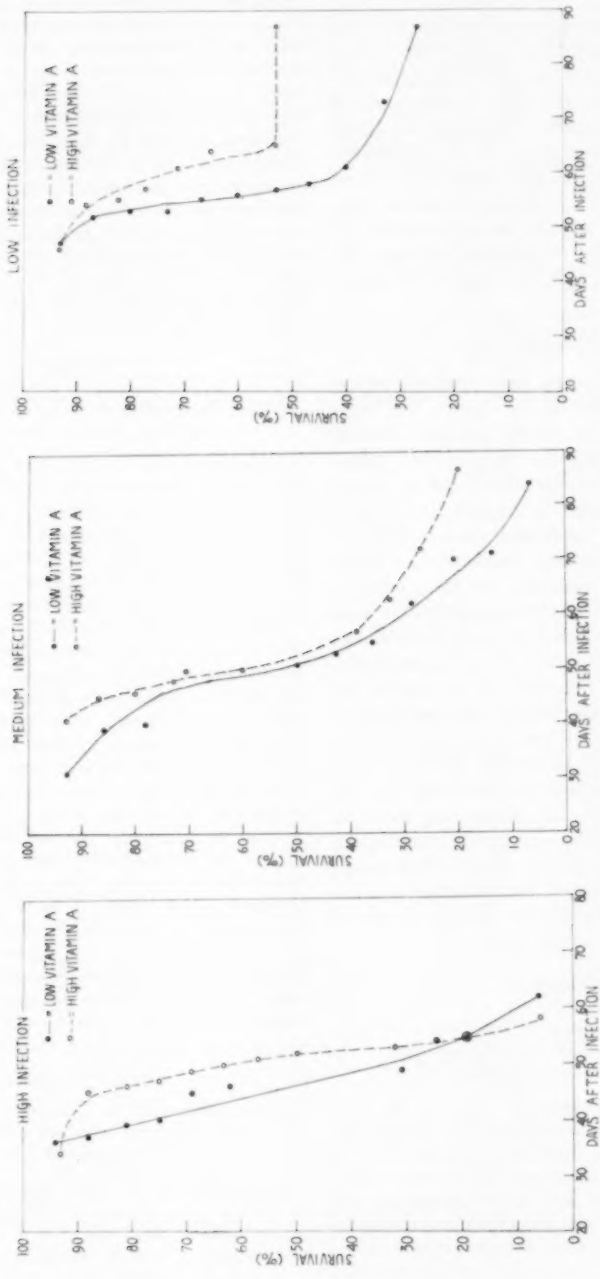

FIG. 2. Survival curves of infected chicks in relation to vitamin A content of diet.

sponse in the chicken closer to that observed for mice.

The striking increase in percentage survival obtained by increasing vitamin A from low to adequate levels merits further study of higher levels. The chicks on the lower of the levels of vitamin A did not appear to be under any stress due to hypovitaminosis A on the basis of growth curve, general behavior, and appearance. These considerations encourage further study of vitamin A as a possible specific dietary factor in the response of chicks to tuberculous infection, despite the discordant results of earlier investigations.

Summary

The effect of dietary fat and vitamin A on the progress of tuberculosis in chicks has been studied. Chicks were placed on experimental diets when two days old and injected intravenously with *M. tuberculosis*, avian strain Kirchberg. The changes in the diet did not alter growth curves of uninfected chicks. Survival time, tissue changes, and biochemical components of serum were studied. For the studies of fat, relatively severe challenging infections were used, leading to the death of more than 90 per cent of the infected animals. With the less severe of such infections, reduction of fat concentration prolonged median survival time and reduced the number of tubercles per tissue section in the spleen. The biochemical changes in serum were correlated with infection but not with diet. In the vitamin A study, the challenging infection included doses that allowed a small percentage of survival of some test groups. Under these conditions, increased levels of dietary vitamin A led to a 26 per cent increase in the percentage of survivors among infected chicks.

Sumario

El Efecto de la Grasa y la Vitamina A en la Alimentación sobre la Tuberculosis Aviaria en los Pollos

Se ha estudiado el efecto de la grasa y la vitamina A en la alimentación sobre la evolución de la tuberculosis en los pollos. A los dos días de nacidos, se impusieron a éstos dietas experimentales y se les inyectaron intravenosamente *M. tuberculosis*, cepa aviaria Kirchberg. Las modificaciones de la dieta no alteraron las curvas del desarrollo de los pollos indemnes. Para los estudios de la grasa, se usaron infecciones provocadoras relativamente graves, que condujeron a la muerte de más de 90 por ciento de los animales infectados. En las menos graves de esas infecciones, la reducción de la concentración de grasa prolongó el tiempo medio de sobrevivencia e hizo bajar el número de tubérculos por corte de tejido en el bazo. Las alteraciones bioquímicas en el suero se correlacionaron con la infección, pero no con la alimentación. En el estudio de la vitamina A, la infección provocadora comprendió dosis que permitieron un pequeño porcentaje de sobrevivencias en algunos de los grupo ensayados. En esas condiciones, el aumento de los tenores de la vitamina A en la alimentación condujo a un aumento de 26 por ciento en el número de sobrevivientes entre los pollos infectados.

Resume

L'effet du régime graisseux et de la vitamine A sur la tuberculose aviaire des poulets

Les auteurs ont étudié l'effet du régime graisseux et de la vitamine A sur les progrès de la tuberculose chez des poulets. Les poulets furent mis à des régimes expérimentaux à l'âge de deux jours et on leur injecta par voie intraveineuse du *M. tuberculosis*, de la souche aviaire de Kirchberg. Les changements de régime ne changèrent pas les courbes de développement des poulets non infectés. On étudia le temps de survie, les changements tissulaires et les composés biochimiques du sérum. Pour étudier les graisses, on utilisa des infections attaquant relativement sévèrement, entrainant la mort de plus de 90% des animaux infectés. Avec les moins sévères de telles infections, la réduction de la concentration en graisses augmenta le temps moyen de survie et réduisit le nombre de tubercules par section de tissu splénique. Les changements biochimiques du sérum furent en rapport avec l'infection mais pas avec le régime. Dans l'étude de la vitamine A, l'infection attaquante comprit des doses qui permirent un petit pourcentage de survie dans certains groupes étudiés. Dans ces conditions, l'augmentation des taux de vitamine A dans le régime conduisit à une augmentation de 26% du pourcentage des survivants parmi les poulets infectés.

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THE SERUM PROTEIN AND LIPOPROTEIN RESPONSE TO TUBERCULOSIS IN CHICKS FED VARIOUS LEVELS OF DIETARY FAT[1,2,3]

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INTRODUCTION

In mammals, the serum proteins and constituent fractions, separated by electrophoresis, are significantly altered by a wide variety of physiologic and pathologic factors. Among these, the effects of experimental infection with *Mycobacterium tuberculosis* have been studied in the rabbit (1), the guinea pig (2), the mouse (3), and the rat (4).

Although the serum proteins of birds have been the subject of several investigations by free (5–7) and zone (8) electrophoresis, these studies have dealt primarily with factors other than pathologic states. Reports are available concerning the effects of vitamin E deficiency (9) and of erythroblastosis (10) on the electrophoretic distribution of serum proteins in the chick.

Since dietary fat level has been reported (11) to influence resistance to experimental infection with *M. tuberculosis* in mice, the present investigation was designed to study the serum protein response in the chick to infection with avian tubercle bacilli; and to assess the possible effects of dietary fat level on this response. Data regarding mortality and tissue reactions to infection are the subjects of other reports (12); those presented here concern the serum protein and lipoprotein responses to infection studied by paper electrophoresis.

MATERIALS AND METHODS

Animals and animal care: The animals were one-day-old white leghorn cockerels and were housed in a heated battery with an initial temperature of 95° to 100°F. The temperature was decreased gradually for four to five weeks, when the animals were transferred to a larger battery at room temperature which varied between 65° and 75°F. Both types of batteries had raised wire floors to prevent reinfection by coprophagy.

Experimental diets: The basal diet contained 24 per cent protein and 1.5 per cent fat and was, by calculation, nutritionally adequate in all other dietary factors. For purposes of variation in fat content, the basal diet (low fat) was supplemented to provide total fat levels of 9.5 per cent (medium fat), 17.5 per cent (high fat), and 25.5 per cent (very high fat). Precise compositions for the basal diet and for the supplementary fats are given elsewhere (12). Feed and water were supplied *ad libitum*, and feed consumption was recorded daily.

Inoculum: The infecting organism was *Mycobacterium tuberculosis*, avian Kirschberg strain. A standard suspension was prepared by diluting twelve- to fourteen-day-old Tween®-albumin cultures to a turbidity permitting 40 to 50 per cent transmission at 600 mμ. This suspension was used or diluted with Tween-albumin as required to produce various levels of infection. Animals were infected intravenously with 0.5 ml. of suspension.

Experimental design: Data presented here were obtained in two experiments. In *Experiment 1*, diets comprised 1.5, 9.5, 17.5, and 25.5 per cent fat. Fat levels were increased by supplementation with either corn oil or coconut oil. Each experimental animal was infected with the standard inoculum, undiluted, as described above.

In *Experiment 2*, three fat levels (1.5, 9.5, and 17.5 per cent) were employed, supplementation with corn oil providing the higher fat concentrations. Equal numbers of animals on each dietary regimen were infected with the undiluted standard suspension or a 1:10 dilution of this suspension. These two infecting inocula for purposes of reference were designated as "High TB" and "Medium TB," respectively.

In both experiments, animals were assigned at random to their respective treatment groups at one day of age and were infected when seven days old. When the infection was well established, as determined by a significant decrease in growth rate (but before morbidity became evident), blood samples were obtained. This procedure was performed twenty-eight and thirty-four days after infection in *Experiments 1* and *2*, respectively.

Analytic methods: Serum was separated from clotted blood samples within four hours after bleeding and was stored at −20°C. until analyzed.

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Aliquots of serum for lipoprotein determination were never frozen and were stored at 5°C. in order to avoid denaturation.

Serum proteins were separated by paper electrophoresis in Durrum type (Spinco) cells fitted with S & S mgl paper strips properly equilibrated with aqueous veronal buffer, pH 8.6, ionic strength 0.075. Optimal resolution required electrophoresis of 30 microliter samples for 20 hours at 5°C., with a constant current of 3 mA applied to each cell. After electrophoresis, the paper strips were processed and stained with methanolic bromphenol blue, described as Spinco procedure B (13). Densitometric analysis was performed with the Spinco Analytrol, model RB.

Serum lipoproteins were separated by paper electrophoresis of 40-microliter samples, with a constant voltage of 200 V/cell for four hours at room temperature. Strips were processed and stained with ethanolic Oil Red O (13), and analyzed by scanning with the Spinco Analytrol. Total lipoprotein concentration was estimated by application of a pseudo-standard (cream) of known fat content to each strip before staining. This procedure was also useful in monitoring the staining capacity of the Oil Red O dye.

Serum protein concentrations were determined colorimetrically by the method of Lowry and associates (14) as modified by Miller (15).

Statistical analysis of data, consisting of analysis of variance according to Snedecor (16), was employed to evaluate the effects of infection and diet upon the parameters studied.

Results

Total serum proteins: The effects of infection and of dietary fat level on the serum proteins are shown in tables 1 and 2. In the uninfected control animals on the various dietary regimens, the total serum protein concentration varied from 3.56 to 4.67 gm. per 100 ml. Although the values were somewhat higher in *Experiment 2*, there was no consistent relationship to dietary fat level in either experiment.

Comparison of control values with corresponding infected groups revealed that infection uniformly induced hyperproteinemia. The response ranged from an increase of 29.5 per cent (4.57 to 6.41 gm. per 100 ml.) in the low-fat regimen in *Experiment 2* to an increase of 57.6 per cent (3.63 to 5.72 gm. per 100 ml.) in the high-fat–coconut oil group in *Experiment 1*. Statistical analysis revealed that this increase in serum protein concentration was significant ($P < 0.05$).

Electrophoretic fractions: Paper electrophoresis, under the conditions used, resulted in the separation of six clearly defined serum protein fractions. The nomenclature adopted for chick serum by Vanstone and co-workers (8) has been used. Alterations produced by infection in the various dietary regimens are shown in tables 1 and 2. The various components are expressed in terms of concentration (gm. per 100 ml.) since this calculation presents, simultaneously, effects of infection on the quantity present as well as on distribution of the total protein among its fractions.

Infection produced significant ($P < 0.001$) changes in four of the protein fractions: albumin, alpha-3 globulin, beta globulin, and gamma globulin. The albumin concentration in uninfected animals varied from 1.61 to 2.16 gm. per 100 ml., values which are equivalent to 42.2 per cent to 49.1 per cent of the total protein. The corresponding range for infected animals was from 0.33 to 0.87 gm. per 100 ml., or 5.3 per cent to 16.2 per cent of total protein. Circulating albumin was thus reduced in all infected groups, the average reduction being 68 per cent. In *Experiment 2* (table 2), in which two levels of infection were induced, the reduction in albumin was more pronounced in the high (average 85 per cent) than in the medium (average 66 per cent) infection groups.

In the case of the gamma-globulin fraction, infection produced significant increases ($P < 0.001$) in all groups. Noninfected controls had gamma-globulin concentrations varying from 0.33 to 0.75 gm. per 100 ml., while the range in infected animals was 1.10 to 2.64 gm. per 100 ml. The average increase for all infected groups was 245 per cent, the increase being less pronounced in the medium (180 per cent) than in the high infection groups (279 per cent).

Alterations in the alpha-3 and beta globulin fractions by infection were similar in direction but somewhat less pronounced than those described for gamma globulin. The increases in these two fractions were also significant ($P < 0.01$). Although the alpha-1 and alpha-2 globulin fractions were also minimally increased by infection, the effect was insignificant. Statistical treatment of the data showed that the effects of infection were not correlated with dietary fat level in either of the two experiments.

Lipoproteins: Protein-bound lipid in chick serum is separable by the techniques used into two fractions, alpha and beta lipoprotein. Pilot experiments, in which parallel strips were stained for protein and lipoprotein, demonstrated that the mobility of the alpha fraction corresponded

TABLE 1

SERUM PROTEINS IN CHICKS FED VARIOUS LEVELS OF DIETARY FAT AND INFECTED WITH M. TUBERCULOSIS, AVIAN STRAIN (Experiment 1)

Fat Level	Level of Infection	Number of Animals	Total Protein	Albumin	Globulin				
					Alpha-1	Alpha-2	Alpha-3	Beta	Gamma
			gm./100 ml.	*gm./100 ml.*	*gm./100 ml.*				
Low	None	10	3.77 (0.24)*	1.85 (0.24)	0.34 (0.06)	0.23 (0.06)	0.56 (0.06)	0.35 (0.12)	0.36 (0.14)
	High	9	5.64 (1.02)	0.77 (0.26)	0.75 (0.18)	0.50 (0.06)	1.35 (0.24)	0.85 (0.38)	1.41 (0.42)
Medium (Corn)	None	10	3.87 (0.34)	1.81 (0.15)	0.27 (0.07)	0.29 (0.06)	0.47 (0.11)	0.45 (0.32)	0.55 (0.40)
	High	10	5.06 (0.85)	0.72 (0.42)	0.75 (0.23)	0.46 (0.06)	1.09 (0.27)	0.59 (0.24)	1.45 (0.59)
Medium (Coconut)	None	9	3.56 (0.27)	1.61 (0.44)	0.38 (0.09)	0.32 (0.01)	0.47 (0.06)	0.30 (0.05)	0.42 (0.16)
	High	8	4.60 (0.79)	0.72 (0.37)	0.71 (0.13)	0.46 (0.13)	1.05 (0.31)	0.56 (0.17)	1.10 (0.37)
High (Corn)	None	9	3.82 (0.42)	1.79 (0.16)	0.39 (0.09)	0.35 (0.04)	0.49 (0.08)	0.34 (0.11)	0.48 (0.31)
	High	6	5.19 (0.41)	0.52 (0.22)	0.78 (0.26)	0.45 (0.10)	1.08 (0.26)	0.76 (0.26)	1.59 (0.39)
High (Coconut)	None	6	3.63 (0.15)	1.62 (0.26)	0.39 (0.17)	0.34 (0.08)	0.47 (0.03)	0.46 (0.13)	0.35 (0.20)
	High	8	5.72 (0.64)	0.53 (0.24)	0.86 (0.12)	0.46 (0.08)	1.45 (0.24)	0.78 (0.22)	1.50 (0.53)
Very high (Corn)	None	6	3.83 (0.11)	1.78 (0.08)	0.43 (0.11)	0.38 (0.08)	0.58 (0.11)	0.32 (0.08)	0.33 (0.10)
	High	6	5.47 (1.34)	0.83 (0.55)	0.83 (0.23)	0.57 (0.30)	1.06 (0.29)	0.56 (0.08)	1.61 (0.49)

* Mean and standard deviation

TABLE 2

SERUM PROTEINS IN CHICKS FED VARIOUS LEVELS OF DIETARY FAT AND INFECTED WITH VARIOUS LEVELS OF M. TUBERCULOSIS, AVIAN STRAIN (Experiment 2)

Fat Level	Level of Infection	Number of Animals	Total Protein	Albumin	Globulin				
					Alpha-1	Alpha-2	Alpha-3	Beta	Gamma
			gm./100 ml.	*gm./100 ml.*	*gm./100 ml.*				
Low	None	15	4.57 (0.56)*	2.03 (0.34)	0.38 (0.07)	0.35 (0.04)	0.70 (0.30)	0.47 (0.11)	0.66 (0.27)
	Medium	11	5.74 (0.78)	0.70 (0.33)	0.76 (0.10)	0.44 (0.11)	1.36 (0.19)	1.01 (0.22)	1.49 (0.42)
	High	13	6.41 (1.72)	0.34 (0.08)	0.59 (0.21)	0.38 (0.08)	1.43 (0.49)	1.25 (0.40)	2.45 (0.77)
Medium	None	11	4.54 (0.75)	2.16 (0.32)	0.45 (0.06)	0.41 (0.05)	0.58 (0.14)	0.40 (0.09)	0.57 (0.15)
	Medium	13	6.45 (0.83)	0.87 (0.63)	0.87 (0.20)	0.52 (0.08)	1.35 (0.27)	1.02 (0.26)	1.86 (0.40)
	High	13	6.16 (0.91)	0.33 (0.16)	0.57 (0.22)	0.36 (0.05)	1.38 (0.25)	1.19 (0.27)	2.36 (0.16)
High	None	15	4.67 (0.83)	1.98 (0.52)	0.43 (0.15)	0.40 (0.08)	0.65 (0.15)	0.47 (0.06)	0.75 (0.82)
	Medium	13	6.57 (0.97)	0.53 (0.22)	0.85 (0.17)	0.47 (0.12)	1.29 (0.24)	1.27 (0.40)	2.17 (0.51)
	High	13	6.92 (1.22)	0.37 (0.11)	0.74 (0.19)	0.47 (0.12)	1.49 (0.32)	1.23 (0.92)	2.64 (0.81)

* Mean and standard deviation

to that of the alpha globulins (principally alpha-1 and alpha-2 globulins) while the beta fraction was associated with the beta and gamma globulins.

Effects of avian tuberculosis on the relative distribution of lipoprotein are shown in table 3. In noninfected animals, protein-bound lipid was predominantly carried in the alpha fraction, the average for the three control groups being 71.0 per cent of the total lipoprotein. Infection with the higher inoculum effected essentially complete reversal of the distribution, reducing the alpha lipoprotein to 33.3 per cent in the three groups. In the medium infection groups, these changes were less pronounced, the average alpha lipoprotein being 54.7 per cent. As a result of these changes, the mean beta/alpha lipoprotein ratio was inverted from a value of 0.43 in

TABLE 3

SERUM LIPOPROTEINS IN CHICKS FED VARIOUS LEVELS OF DIETARY FAT AND INFECTED WITH VARIOUS LEVELS OF M. TUBERCULOSIS, AVIAN STRAIN (Experiment 2)

Fat Level	Level of Infection	Number of Animals	Protein-bound Lipid			Beta/Alpha Ratio
			Beta	Alpha	Total	
			per cent	*per cent*	*mg./100 ml.*	
Low	None	15	31.1 (5.6)*	68.9 (5.9)	829 (138)	0.46 (0.12)
	Medium	13	49.4 (15.2)	50.6 (15.2)	588 (139)	1.01 (0.55)
	High	13	75.9 (13.0)	24.1 (13.6)	674 (239)	2.77 (1.34)
Medium	None	12	29.1 (7.8)	70.9 (7.8)	925 (107)	0.44 (0.21)
	Medium	13	44.1 (9.3)	55.9 (9.3)	637 (153)	0.85 (0.36)
	High	14	66.6 (18.3)	34.2 (18.7)	762 (381)	1.73 (0.96)
High	None	14	26.7 (6.6)	73.3 (5.3)	820 (137)	0.38 (0.08)
	Medium	14	42.3 (10.0)	57.7 (10.0)	591 (139)	0.81 (0.45)
	High	14	58.4 (14.4)	41.6 (15.0)	629 (144)	1.49 (0.87)

* Mean and standard deviation

the uninfected groups to 0.89 in the medium infection and 2.00 in the high infection groups. Neither fat level nor infection had a consistent effect on the total protein-bound lipid.

Examination of the beta/alpha ratios (table 3) reveals two trends which are pertinent. The degree of inversion caused by infection appears to be related to the magnitude of infecting inoculum, being much more pronounced at the high than at the medium infection levels. Also, this change in distribution became less pronounced with increasing dietary fat.

Statistical analysis demonstrated that the effect of infection on the distribution of lipoprotein was highly significant ($P < 0.001$), but effects on this response of diet and of inoculum size, although biologically meaningful, were not significant.

DISCUSSION

The characteristics of serum protein changes in experimental tuberculosis vary with species of host. Seibert and Nelson (1) reported a decrease in albumin and an increase in beta globulin in rabbits infected with the bovine variety. Serum protein was slightly increased. In guinea pigs infected with the human variety, decrease in albumin and increases in gamma globulin and total protein have been observed (2). Infection of mice with the human strain resulted in increases in the alpha-1 and alpha-2 globulins and a slight decrease in albumin, while the total protein remained unchanged (3). In the rat infected with an attenuated (BCG) strain, the sole response was a decrease in the alpha-1 globulin fraction (4).

The results concerning serum proteins and their electrophoretic patterns in uninfected control animals agree well with those reported by Vanstone and associates (8) for chicks of the same age and sex. Infection of the chick with *M. tuberculosis*, avian strain, resulted in significant decrease of albumin and increases of alpha-3, beta, and gamma globulins, with an increase in total protein. The mean decrease (68 per cent) in albumin and increase (245 per cent) of gamma globulin in infected chicks are more pronounced than the comparable changes reported for other host species. In this connection, it is of interest to note that the magnitude of change in serum protein fractions appears to be greatest in those species which are more susceptible to the strains of organism used.

Miller and Bale (18) have presented direct evidence that the liver is the site of synthesis of all albumin and probably of all of the alpha and beta globulins in the rat. Presumptive evidence is available which would indicate that the liver also is a source of albumin in the chicken (19). The marked decrease in albumin observed in the infected chicks may be attributable to liver damage, since this organ is one of two primary sites of localization of the infection in birds (20). Since, in contrast, gamma globulin is formed in extrahepatic tissues (21), the increase observed in this fraction cannot be related to liver dam-

age, but follows the classic relation of increase in gamma globulin with the production of antibody (22). Wostman (23) has shown that increase in gamma globulin is the sole result of exposure of chicks reared in a germ-free environment to various bacterial species. Interpretation of changes in the alpha and beta globulins is more complex, and is not possible with present information.

Although Vanstone and associates (8) illustrate the presence of protein-bound lipid in the globulin fractions, the distribution of the lipoproteins was not described quantitatively. The present results would indicate that the lipoprotein pattern in the uninfected chick resembles that in the dog (17) in that most of the protein-bound lipid in both species is carried by the alpha globulins.

Serum lipoproteins in experimental tuberculosis have been studied by Sher and co-workers (24) in the guinea pig infected with the H37Rv strain of bacilli. Although substantial changes were noted in the protein and protein-bound carbohydrate fractions, the lipoproteins were totally unaffected by infection. This result is not surprising in view of the fact that no changes were noted in the alpha and beta globulins (to which the lipid is bound) in their experiment. These observations are in sharp contrast, however, with the complete reversal of the beta/alpha lipoprotein ratio noted in the infected chicks of the studies reported here. Although the precision of the lipoprotein separations was not adequate to allow lipid/protein ratio calculations for each protein fraction, decrease in alpha lipoprotein concurrent with increase in alpha globulin suggests that alterations occur in the synthesis or mobilization of alpha lipoprotein in infection. This is perhaps related to the problem of liver damage discussed above.

Although modest effects of dietary fat level upon survival of chicks infected with *M. tuberculosis* are reported elsewhere (12), these effects are not reflected in the response of the serum proteins and their constituent fractions studied by paper electrophoresis.

Summary

The effects of experimental tuberculosis upon the electrophoretic fractions of serum proteins and lipoproteins of the chick have been studied. Infection induced hyperproteinemia with a decrease in albumin and increases in alpha-3, beta, and gamma globulins.

Alteration of protein-bound lipid distribution by infection was characterized by increase of the beta lipoprotein fraction and of the beta: alpha lipoprotein ratio.

Variation of dietary fat content from 1.5 to 25.5 per cent failed to influence these responses in infected animals.

Sumario

La Respuesta en Proteínas y Lipoproteínas del Suero a la Tuberculosis en los Pollos Alimentados con Varios Tenores de Grasa Dietética

Se han estudiado los efectos de la tuberculosis experimental sobre las fracciones electroforéticas de las proteínas y lipoproteínas del suero sanguíneo del pollo. La infección indujo hiperproteinemia con disminución de la albúmina y aumentos de las globulinas alfa-3, beta y gamma.

La alteración de la distribución de lípidos proteinofijos por la infección se caracterizó por aumento de la fracción de lipoproteína beta y de la proporción de lipoproteína alfa:beta.

La variación del contenido de grasa dietética de 1.5 a 25.5 por ciento no afectó estas respuestas en los animales infectados.

Resume

La réponse des protides sériques et des lipoprotides à la tuberculose, chez des poulets nourris avec des quantités variées de graisses alimentaires

Les auteurs ont étudié les effets de la tuberculose expérimentale sur les fractions électrophorétiques des protides sériques et des lipoprotides du poulet. L'infection entraina de l'hyperprotidémie avec une diminution de l'albumine et une augmentation des globulines alpha-3, bêta et gamma.

Le changement par l'infection, de la distribution de lipides liés aux protides fut caractérisé par l'augmentation de la fractior bêta des lipoprotides et du rapport bêta-alpha des lipoprotides.

Une variation du taux des graisses du régime, de 1,5 à 25,5%, n'arriva pas à influencer ces réponses chez les animaux infectés.

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Case Reports

RESPONSE OF PULMONARY NOCARDIOSIS TO TREATMENT WITH MASSIVE DOSES OF PENICILLIN INTRAVENOUSLY[1,2]

Report of a Successfully Treated Case with Four-Year Follow-up Observation, together with Review of the Literature

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INTRODUCTION

Systemic infection with microorganisms of the genus Nocardia has been recognized as a disease of high mortality since the first clinical description by Eppinger in 1890 (1). The ineffectiveness of treatment prior to the chemotherapeutic and antimicrobial era has been emphasized in several reviews (2–6). The sulfonamides are now known to exhibit significant inhibition of these organisms *in vitro* and in animal and human infections (7–23). The broad-spectrum antimicrobials are effective *in vitro* (8, 9, 23, 24) although they have been used infrequently in human disease (22, 25, 26). In contrast, almost all strains of Nocardia are highly resistant to penicillin *in vitro* and when used in the usual doses in man (5, 12, 22, 27, 28).

The present report is concerned with the unexpected and dramatic response of a patient with extensive pulmonary nocardiosis to the administration of massive doses of penicillin G intravenously. A total of 2.5 billion units of penicillin was given to a young woman with nocardiosis of the lungs, ribs, lymph nodes, and chest wall following failure to respond to a large variety of broad-spectrum antimicrobials, several sulfonamides, amphotericin B, sulfoxone sodium, isoniazid, and penicillin in ordinary dosage. The favorable response in the face of resistance *in vitro* suggests the possible use of penicilllin in massive dosage for those patients who fail to respond to adequate trials with the sulfonamides and the broad-spectrum antimicrobials. The low toxicity and high solubility of crystalline penicillin offer dosage possibilities unattainable with any other therapeutic agent.

[1] From the Department of Medicine, University of Kentucky Medical Center, Lexington, Kentucky; and Hunterdon Medical Center, Flemington, New Jersey.

[2] Aided by a Grant-in-Aid from Ortho Research Foundation.

CASE REPORT

First Admission

A 33-year-old white housewife was first admitted to the Surgical Service of the Hunterdon Medical Center in Flemington, New Jersey, on November 3, 1956, because of swelling of two weeks' duration in the anterolateral aspect of the left side of the neck. This was accompanied by coryza, rhinitis, malaise, and fatigue. The swelling had become larger, more tender, and more erythematous in the two days prior to admission. Her subsequent clinical course and treatment are summarized in figure 1. At the time of the present report (February, 1961), the patient has been followed for a total of four years from the onset of her illness.

Past medical history: The patient underwent tonsillectomy and adenoidectomy at the age of seven and an appendectomy at the age of 14. She received sulfadiazine in 1948 for tonsillitis, without untoward reaction. The patient had no known exposure to unusual dusts or soils or sick animals.

Physical examination: The temperature on admission was 98.8°F., respirations 20 per minute, pulse 80 per minute, and blood pressure 145 systolic, 80 diastolic in mm. of mercury. Weight was 137 pounds. The patient was well developed and well nourished. She was edentulous, and wore upper and lower dentures. Over the anterolateral left neck, a 4- by 3-cm. firm, tender, slightly fluctuant, freely movable mass was palpable. The major swelling was at the level of the thyroid cartilage adjacent to the anterior border of the left sternocleidomastoid muscle. Erythema and tenderness extended from the angle of the jaw on the left to the level of the second intercostal space. The lungs were clear to percussion and auscultation. There was no general lymphadenopathy. The remainder of the examination was entirely normal.

Laboratory data: Urinalysis was normal. Hemoglobin was 11 gm.; the leukocyte count, 8,700 per cu. mm. with 84 polymorphonuclear leukocytes, 8 lymphocytes, 7 monocytes, and 1 eosinophil. The hematocrit was 37 per cent and the erythrocyte sedimentation rate, 45. The fasting blood sugar

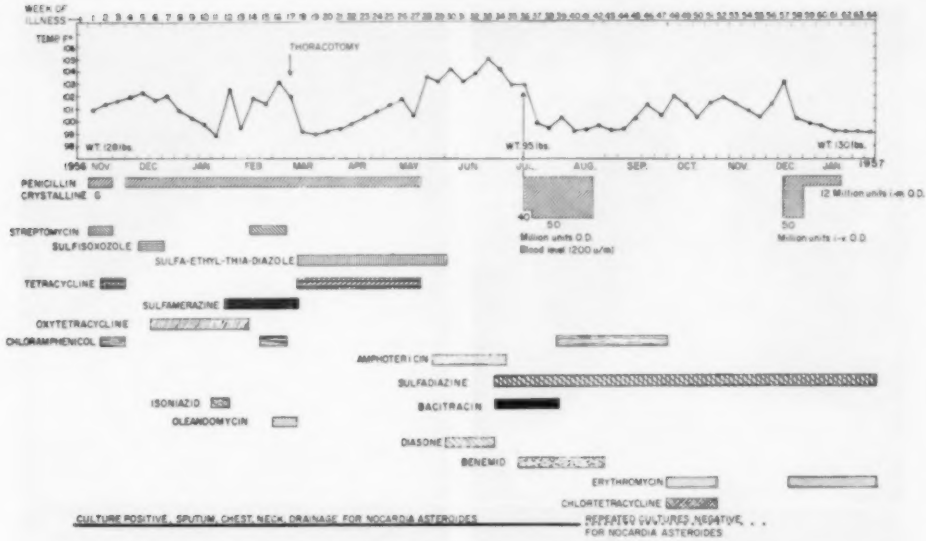

FIG. 1. Summary of patient's clinical course and treatment from November, 1956, to January, 1957.

was 76 mg. per 100 ml. Roentgenograms of the jaw, dated November 5, 1956, were normal.

Course in hospital: The neck mass was thought to be an infected branchial cyst. The patient was treated with penicillin (4.0 million units) and streptomycin (1.0 gm.) daily. Despite this treatment, she manifested a low-grade fever and a slight increase in the fluctuation and erythema of the skin in the affected area. On November 12, 1956, incision and drainage were performed with removal of a small amount of purulent material and necrotic tissue which, on subsequent culture and microscopic study, showed *Nocardia asteroides* (*see* laboratory and roentgenographic findings). Penicillin and streptomycin were discontinued, and the patient was started on chloramphenicol and tetracycline, 1.0 gm. of each per day. On November 17, 1956, the patient was discharged on tetracycline, 250 mg. every six hours.

Second Admission

The patient was admitted to the Medical Service of the Hunterdon Medical Center on November 24, 1956, because of continuing drainage from the biopsy site over the left anterolateral neck.

Physical examination: The temperature, pulse, respiration, and blood pressure were all normal. There was a fungating wound over the anterior left cervical region with marginal induration and erythema. There was no lymphadenopathy. The remainder of the examination was unremarkable.

Laboratory and roentgenographic findings: A chest film obtained in 1950 was available, was reviewed, and showed no abnormalities. A postero-anterior roentgenogram of the chest (figure 2*A*), dated November 5, 1956, revealed a moderately well circumscribed, triangular infiltration in the lateral aspect of the right lung field, at the level of the fifth to the seventh posterior ribs. No significant differences were noted on a postero-anterior roentgenogram of the chest dated November 26, 1956.

Frequent serial urinalyses throughout the patient's illness were normal in all respects.

Hemoglobin on admission was 10.7 gm. and the leukocyte count was 9,000 per cu. mm. with 78 polymorphonuclear leukocytes, 18 lymphocytes, and 4 monocytes. The hematocrit was 36 per cent and the erythrocyte count, 3,790,000 per cu. mm. Serum albumin and globulin and urea nitrogen were normal on several occasions.

Culture of the sputum for tubercle bacilli showed no growth on three occasions. Culture of the sputum and neck drainage was consistently positive for *Nocardia asteroides*.

Mycologic findings: The organism isolated consistently and repeatedly from the neck and chest-wall drainage, before the initiation of large doses of penicillin, had the characteristics of *Nocardia asteroides*. Tissue sections showed gram-positive branching hyphae invading surrounding tissue which exhibited a granulomatous response. The criteria recently re-emphasized for differentiation from *Actinomyces bovis* were satisfied (21).

The strain of Nocardia isolated in the patient showed resistance *in vitro* to a large number of antimicrobial agents, most of which were tried subsequently *in vivo*. The only agent not first

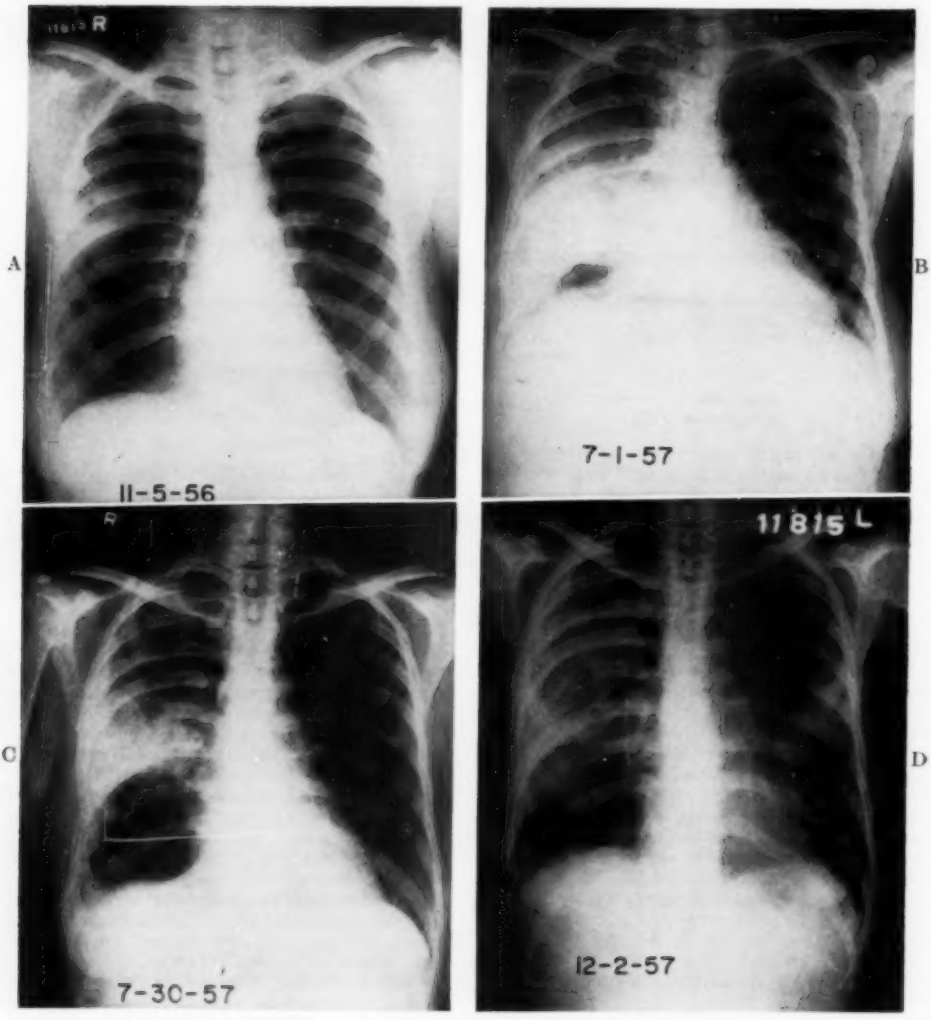

FIG. 2. Selected roentgenograms obtained during the acute phases of the patient's illness.

tested *in vitro* was sulfoxone sodium. It is indicated in table 1 that, except for some of the broad-spectrum antimicrobials, the organism was resistant to the usually attainable concentrations of most antimicrobial agents. The inhibiting concentrations for nystatin, amphotericin B, and sulfaethyl-thiadiazole were higher than those usually achievable in blood.

Samples of soil and dust from the patient's home were cultured for *Nocardia asteroides* with negative results.[3]

[3] Communicable Disease Center, Laboratory Branch, Chamblee, Georgia.

Course in hospital: Following the report of a culture positive for *Nocardia asteroides*, the patient was treated with sulfisoxazole, 6 gm. daily; potassium iodide, increasing drop-wise dosage; and penicillin, orally, in a dose of 10 million units daily. Reference should be made to figure 1 for a diagrammatic representation of the course of treatment with each drug and the relationship of one drug course to the other. Potassium iodide was stopped on December 2, 1956, following a rise in temperature to 104°F. and other signs of iodism (salivation, rash, metallic taste, swelling of salivary glands). On December 9, 1956, the patient developed a diffuse erythematous rash with puffiness

of the eyelids, and this was associated with a depression of her total leukocyte count. This response was attributed to sulfisoxazole. When this drug was discontinued, the rash cleared slowly and the leukocyte count returned to normal. During December, 1956, the patient slowly lost weight, showed a temperature rise between 100° and 102°F. daily, and noted continuing drainage from the neck wound. Cultures of the sputum and neck remained positive for Nocardia. During this period, oxytetracycline was given in a dosage of 2 to 4 gm. per day without appreciable effect.

In early January, the patient developed another fluctuant abscess below and behind the previous drainage site in the left side of the neck. Incision and drainage were carried out, and the material obtained was positive for *Nocardia asteroides* on microscopy and culture.

In the latter part of January, 1957, rales were audible over the angle of the right scapula, and the chest roentgenogram showed an increase in the density of the pulmonary infiltrate. Slight clubbing of the fingers was noted for the first time. In late January, following subsidence of the rash and fever attributed to sulfisoxazole, sulfamerazine was started in a dose of 1 gm. every six hours. In the middle of February, the patient developed a fine, generalized erythematous rash, and her leukocyte count again dropped to 2,500 per cu. mm. with a normal differential count. Sulfamerazine was discontinued early in March with prompt return of the leukocyte count to normal and disappearance of the rash.

During this interval, a trial of isoniazid (300 mg. a day) was instituted for a period of about ten days without effect on the clinical course or the fever. Because of the evidence of generalized rash and depression of the leukocyte count on several sulfonamides and because the lesion was relatively stable and localized roentgenographically, an attempt was made at thoracotomy and segmental resection early in March. The patient was treated preoperatively with oleandomycin, chloramphenicol, streptomycin, and the reinstitution of sulfamerazine. At operation it was quickly evident that there was marked involvement of the chest wall, including the ribs. The pleural space was not entered. Histologic examination of the resected section of rib revealed *Nocardia asteroides*, and cultures taken at the time of operation produced a luxuriant growth of this organism.

Postoperatively, the patient was placed on tetracycline, 2 to 3 gm. per day, and sulfaethylthiadiazole in a dosage of 8 to 12 gm. per day. One and a half million units of nystatin were given daily with the tetracycline. On this regimen, the patient's temperature dropped somewhat during late March and early April. Her appetite and general appearance improved and she slowly gained 5 pounds in weight. The operative chest wound, however, continued to ooze gelatinous material, and a probe could be introduced into a tract in this wound for 5 to 6 cm. The patient at this time experienced increasing depression because of a very unstable family situation. To help her emotionally, she was permitted to go home in mid-April for a brief period, while continuing the above medications. She was seen frequently in the outpatient department and showed little change in status. The neck and chest wounds continued to require daily dressings.

TABLE 1

SUSCEPTIBILITY STUDIES* NOCARDIA ASTEROIDES, PATIENT M. K. FROM SPUTUM, CHEST WALL, AND LYMPH NODE

Susceptible to		Resistant to	
Drug	Concentration per Ml.	Drug	Concentration per Ml.
Amphotericin B†	4 γ	Bacitracin	20 units
Chloramphenicol	30 γ	Isoniazid§	5 γ
Chlortetracycline	30 γ	Neomycin	30 γ
Erythromycin	10 γ	Nitrofurantoin	100 γ
Nystatin†	40 units	Novobiocin	100 γ
Oxytetracycline	30 γ	Oleandomycin	15 γ
Sulfanilamide (sulfaethylthiadiazole)‡	125 γ	*p*-Aminosalicylic acid§	10 γ
Tetracycline	30 γ	Penicillin	10 units 6 γ
		Polymyxin B sulfate	30 γ
		Streptomycin	100 γ
		Sulfadiazine	250 γ
		Sulfisoxazole	100 γ

* Disc method used except for amphotericin B, nystatin, sulfaethyl-thiadiazole, PAS, and isoniazid.

† Performed at Squibb Institute for Medical Research, courtesy of G. Hildick-Smith, M.D., Associate Director.

‡ Performed at Smith, Kline and French Laboratories, Philadelphia, courtesy of J. D. Farquhar, M.D., Medical Department.

§ Performed through courtesy of Mr. Frank Petrik, Bacteriologist, Homer Folks Tuberculosis Hospital, Oneonta, New York.

On May 6, 1957, the patient consented to readmission because of a change in the drainage from the thoracotomy incision from a clear to a dark and bloody material. Examination at this time revealed normal vital signs, except for a temperature of 101.8°F. She was apprehensive and depressed. She appeared acutely and chronically ill. Her weight had gradually fallen to 112 pounds from 137 on admission. There were dullness to percussion and diminished breath sounds over the right upper lung field. The operative incision drained dark, bloody material through a small

opening just above the wing of the scapula. A roentgenogram of the chest revealed a destructive lesion of several ribs and a diffuse "ground glass" haze over the entire upper right lung, above the level of the eighth posterior rib.

On May 10, 1957, a course of amphotericin B[4] was initiated with daily infusions of 50 mg. until June 4, 1957. With each infusion, the patient experienced chills, fever, nausea, and vomiting. These symptoms were partially ameliorated by premedication with salicylates and diphenhydramine. The localized lesion in her neck appeared to be healing; but the chest wound, although somewhat cleaner, continued to drain gelatinous material. The hemoglobin decreased slowly to 6 gm., and the patient required several transfusions. *Nocardia asteroides* was still easily cultured from the chest wall and the neck sites.

On June 5, 1957, the dose of amphotericin B was changed to 75 mg. intravenously every other day. At this time, sulfoxone sodium, 0.3 gm. three times daily, was initiated without appreciable clinical effect. Amphotericin B was discontinued on June 27, 1957. During this interval, the patient exhibited a progressively deteriorating course. By June 15, 1957, the thoracotomy scar had broken down along its entire length of 24 cm. The patient continued to have nausea, and her temperature rose daily to 103° and 104°F.

By the end of June, the hemoglobin had fallen to 4 gm. despite further transfusions. Cough and expectoration increased, and copious wound drainage continued. Peripheral edema was now noted for the first time and, in addition, hepatomegaly.

The patient demonstrated increasing mental confusion. Her clinical situation was considered desperate. She was started on sulfadiazine, 6 gm. a day (despite rash and leukopenia with other sulfonamides), and bacitracin, 6,000 units a day, intramuscularly. Sulfadiazine blood concentrations of 10 to 12 mg. per 100 ml. were achieved.

On this regimen, the patient worsened. By July 1, 1957, she was markedly lethargic. The entire thoracotomy scar was edematous, erythematous, and firm, and exhibited multiple draining fistulas. A probe could be introduced into the chest wound to a depth of 15 cm. A posteroanterior roentgenogram of the chest (figure 2B) revealed transverse cardiac enlargement. There was a diffuse haze over the major portion of the right hemithorax and obvious irregularity of the outlines of the fourth, fifth, and sixth ribs posteriorly.

On July 4, 1957, a thoracentesis yielded 150 ml. of slightly turbid, straw-colored fluid, which had the characteristics of a transudate and was negative on culture for Nocardia.

During the first two weeks of July, auscultation revealed a harsh, blowing, systolic murmur at the apex, transmitted along the left sternal border. The ventricular rate was 120. Clinical and roentgenographic transverse enlargement of the heart persisted. The patient was digitalized, and mercurial diuretics and transfusions of packed erythrocytes were administered.

During this interval, the patient exhibited transient abdominal distention, joint pains, and frequent blood-tinged expectoration. Cough was uncontrollable by the usual means. On July 11, 1957, a new abscess appeared below the lower end of the thoractomy scar. The previous sites continued to drain profusely. Multiple subcutaneous fistulas were present.

The patient now weighed 95 pounds, her hemoglobin was 5 gm., and her temperature was rising daily to 103°F. She was semistuporous and confused.

Beginning on July 5, 1957, 50 million units of penicillin G in 500 ml. of 5 per cent glucose in water were administered intravenously each day. One-half gram of probenecid was given orally three times daily. The temperature dropped within forty-eight hours. The patient improved markedly over the next two weeks. The violent episodes of coughing with blood-tinged expectoration ceased. She became oriented, was able to eat again and to respond to her surroundings. Fourteen days after the start of high doses of penicillin, culture of wound drainage and sputum were negative for Nocardia for the first time. A nonhemolytic *Staphylococcus aureus*, susceptible to chloramphenicol, was cultured from the wound. Bacitracin was discontinued and chloramphenicol instituted.

The patient remained afebrile following institution of massive penicillin intravenously. The lower end of the chest wound showed slow healing, a small amount of clear yellow discharge coming from the upper end. On July 21, 1957, air was expelled through the large posterior chest wound following cough, indicating the presence of a bronchocutaneous fistula. By July 28, 1957, the right lung was clear to auscultation. The patient's appetite and sense of well-being improved progressively and she requested that she be placed in a double room, since she felt so much better.

On July 31, 1957, cultures of sputum, neck wound, and chest wounds revealed no evidence of *Nocardia asteroides*. Roentgenograms (figure 2C) revealed return of the heart size to normal, with marked decrease of the hazy infiltration over the right hemithorax. Further irregularity of the rib margins on this side was noted, as well as beginning regeneration of the right seventh posterior rib. The chest wound continued to drain moderate amounts of clear yellow fluid. By August 4, 1957, the harsh, apical systolic blow, peripheral edema, and dyspnea had disappeared entirely.

On August 8, 1957, the hemoglobin had risen to 10.2 gm. and the leukocyte count was 9,200, with a normal differential. By August 18, 1957, only one small drainage site persisted in the chest wall scar, and no subcutaneous swelling in other areas was present. The blood urea nitrogen and urinalysis continued normal.

[4] Supplied through the courtesy of Dr. Galvin Hildick-Smith, Associate Medical Director, Squibb Institute for Medical Research, New Brunswick, New Jersey.

During the last week of August, the patient noted the onset of recurrent edema and pain in both lower limbs which was poorly localized and associated with tenderness over both tibia and the dorsum of both feet. She complained of the daily penicillin infusions, and this medication was discontinued. The patient had received a total of 1.5 billion units of penicillin G up to this time. The blood concentration of penicillin at the midpoint of the daily infusion of 50 million units was 1,200 units per ml.[5]

Within two weeks of the discontinuation of penicillin, a gradual return of fever was noted despite continuance of chloramphenicol (2.0 gm.) and sulfadiazine (8.0 gm.) daily. However, the patient's clinical state otherwise continued to improve. The pain in the extremities disappeared. Her weight rose slowly to 112 pounds. The neck wound was completely healed. The chest wound drained very little, but probing was possible to a depth of 12 to 15 cm. The leukocyte count during September was consistently at 15,000 to 25,000 per cu. mm., with a marked shift of the differential count to the left. Culture of the chest wound continued negative for Nocardia, but positive for *Staphylococcus aureus* (hemolytic)—now resistant to chloramphenicol. Despite evidence of resistance *in vitro*, erythromycin, 2.0 gm.; and chlortetracycline, 2.0 gm. a day, were initiated in attempts to control the staphylococcal infection. These were without effect on her fever or clinical course. A ten-day trial of oleandomycin likewise did not appear to alter her course or influence the ease with which *Staphylococcus aureus* was cultured from her chest wound.

During October, there was no appreciable change, and all drugs were discontinued except sulfadiazine, 6 gm. daily. From November to early December, the course was characterized by slow deterioration of the good response obtained with penicillin treatment during the previous summer and fall. Gradual return of fever, cough, weight loss, pain in the extremities, and pulmonary hypertrophic osteoarthropathy was noted. Increased difficulty in handling her emotional problems required occasional out-of-hospital passes.

On December 1, 1957, after returning from a three-day pass, the patient was noted to have a temperature of 102°F. and an intractable cough productive of moderate amounts of purulent yellow sputum. A roentgenogram of the chest dated December 2, 1957 (figure 2D) revealed a poorly circumscribed infiltration in the left lung beneath the fourth and fifth anterior ribs as well as a persistent infiltrate in the right.

The leukocyte count was 19,000. Sputum culture revealed *Diplococcus pneumoniae*, but was negative for *Nocardia asteroides*. The patient had been receiving sulfadiazine. On December 4, 1957, she was again started on penicillin (50 million units) and erythromycin, (2.0 gm.), both intravenously each day. An additional 700 million units of penicillin were thus given. A dramatic drop in temperature and increase in well being were again noted. She was continued on this regimen for about two weeks and then sulfadiazine (4.0 gm.) and intramuscular penicillin (12 million units a day) were substituted for the intravenous medications. She continued to make rapid and excellent progress, remaining completely afebrile, with continued negative cultures from the small chest wound opening. Her weight gradually rose to 115 pounds.

The intramuscular penicillin was discontinued and she was discharged on February 8, 1958, still receiving oral sulfadiazine (6 gm. per day). A roentgenogram at this time revealed nearly complete clearing of the left pulmonary infiltration. Further irregularity and mottling of the posterior right ribs was evident.

By February 11, 1958, the bronchopleural cutaneous fistula had closed. The patient's weight was 121 pounds, and she felt well. By March 6, 1958, the chest wound had completely healed. Her daily temperature continued normal, the lungs were clear, and the patient was free of cough.

By May, 1958, the patient was at full activity and asymptomatic. The only physical finding was recurrent and transient fine rales over the posterior right hemithorax, just beneath the curved thoracotomy scar. She was continued on sulfadiazine, 1.0 gm. three times daily.

In July, 1958 (on a full schedule of activities as a housewife and mother), she weighed 131 pounds and was completely asymptomatic. Examination revealed some diminution of the breath sounds in the upper half of the right lung posteriorly. Clubbing of the fingers and toes was still present, but less marked. Laboratory studies at that time: urinalysis—specific gravity 1.023; pH 6.5, negative for sugar, albumin, and acetone; hemoglobin, 14.6 gm.; leukocyte count, 6,600 per cu. mm. with 73 polymorphonuclear leukocytes, 7 bands, 16 lymphocytes, and 2 basophils. The hematocrit was 46 per cent.

The patient has remained completely well. Her present weight (November, 1960) is 140 pounds. During the interval from 1958 to the present, roentgenograms have revealed (figure 3) virtually complete clearing of the density in the right lung. The left pulmonary infiltrate has cleared completely. Regeneration has occurred in the fourth, fifth, and sixth posterior ribs on the right side. These areas have become smoother and more dense, but over recent months have changed not at all.

Discussion

Nocard (29) in 1888 isolated an aerobic acid-fast organism from cattle with a disease of lymph nodes known as bovine farcy. Trevisan (30) ap-

[5] Performed through the courtesy of Mr. Anthony Abbey, American Cyanamid Company, Princeton, New Jersey.

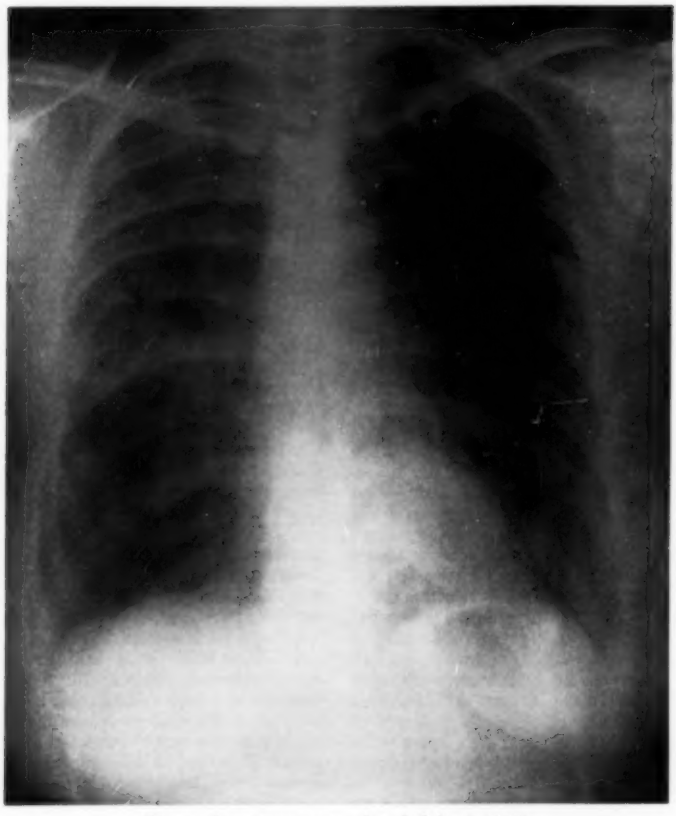

FIG. 3. Roentgenogram dated July 5, 1960.

plied the term Nocardia to this group of organisms and they have since come to be classified among the Actinomyces (31). More than 30 strains have been identified. The one most commonly pathogenic for humans is *Nocardia asteroides*. They are ubiquitously distributed and may infect domestic animals as well as man (32–36).

The high mortality and therapeutic difficulties of systemic nocardiosis, particularly with pulmonary and central nervous system involvement, have been emphasized in all reports in the past forty years (2–6, 19, 22). Gardner and Henrici (2), in 1921, reviewed 25 cases and added one of their own. Those patients were treated empirically with potassium iodide, thymol, and X-radiation, often combined with surgical drainage. The only patient who recovered in this series had Madura foot, a localized form of the disease. Gardner and Henrici's own case was that of a 31-year-old woman with pulmonary involvement who apparently improved with autogenous vaccine. In a later review (5), it was pointed out that two additional patients had recovered in the period prior to 1921, one following thoracotomy and drainage and the other following treatment with potassium iodide.

The inhibitory effect of the sulfonamides on both the aerobic and anaerobic forms of the Actinomyces was demonstrated *in vitro* in 1941 (7). Sulfadiazine, sulfathiazole, and sulfanilamide were all found to be effective. The first successful use of sulfadiazine for nocardial infection was reported in 1943 in a patient with a localized abscess (37). One year later, Benbow, Smith, and Grimson (3) obtained beneficial effects in two patients, using sulfanilamide. Sul-

fadiazine has now come to be regarded by most writers as the drug of choice in the treatment of systemic nocardiosis (8, 14, 19, 22). It has been shown to be highly effective in mouse protection tests (7–9, 11), and most of the successful clinical responses have been reported following its use. Halde and Newstrand (9) demonstrated a primarily bacteriostatic action of the sulfonamides on 34 strains of Nocardia, most of which were responsive *in vitro*. They found sulfamerazine to be most effective. This investigation also pointed out the effectiveness *in vivo* of diasone in mice. Sulfisoxazole has been used successfully in one case (38). A combination of sulfadiazine and one of the broad-spectrum antimicrobials has been suggested as the present optimal therapy (21, 22). However, even with the sulfonamides, the lack of parallel between the susceptibility studies *in vitro* and the effectiveness *in vivo* is noteworthy (8, 11).

Even after the introduction of the sulfonamides, the mortality of nocardiosis continued to be high. Cruz and Clancy (5), in 1952, reviewed forty cases in detail; nine of the patients recovered. Six of these recoveries were attributed to the use of sulfonamides, combinations of antimicrobials, and surgical drainage. Ballanger and Goldring (6) collected 95 cases from the world literature; many of the patients had been treated with sulfonamides and antimicrobials, with an over-all mortality rate of 68 per cent. Peabody and Seabury (22) considered 5 of their 16 patients to be cured by the use of the sulfonamides. Clinical failures have been reported with sulfadiazine (28, 39, 40), though most strains isolated from patients have been susceptible to less than 10 mg. of sulfadiazine per 100 ml. of blood (12, 16, 22).

In contrast to the relative effectiveness of the sulfonamides, many studies have indicated a high degree of resistance of most strains of Nocardia to penicillin (8, 9, 11, 27). Drake studied 5 strains of *Nocardia asteroides* and found all highly resistant. The most susceptible strain required a level of 1,000 γ per ml. to achieve even partial inhibition of growth (27). Resistance was attributed to the presence of a penicillinase.

In those instances in which susceptibility of the organism to penicillin was tested *in vitro* after isolation from patients with the disease, a high degree of resistance has usually been encountered. Strains have been found resistant *in vitro* to concentrations of 50 to 1,000 units of penicillin per ml. (8, 11, 12, 26–28). Hager, Migliaccio, and Young (16) studied two patients whose organisms were unusual in showing susceptibility to penicillin at concentrations of 0.004 to 0.008 γ per ml. and 0.015 to 0.03 γ per ml.

The clinical results with penicillin have been most unsatisfactory and have correlated well with the *in vitro* ineffectiveness. In a recent extensive review of 95 cases from the world literature, no patient recovered who had received penicillin alone (6). Several patients did recover following the use of penicillin with streptomycin. Virtually all of the remaining recoveries involved the use of sulfadiazine together with penicillin and/or one of the broad-spectrum antimicrobials.

There are a few reports in which clinical effectiveness was attributed to penicillin. All of the patients received sulfonamides at one time or another. Calero (39), in 1946, reported the successful treatment of a 16-year-old girl with pulmonary nocardiosis and multiple fistulas by using 20,000 units of penicillin every three hours for a total of 7.5 million units. The patient had exhibited prior failure of response to three courses of sulfadiazine and penicillin used together. Shaw, Holt, and Ray (10) used 50,000 units of penicillin intravenously a day for ten days for a patient with pulmonary nocardiosis and draining chest sinuses. There was temporary improvement and then a relapse which was retreated with 50,000 units of penicillin intramuscularly every three hours for one week, with good response. This patient, however, was also treated with sulfadiazine, and the writers believed that it was the effective agent.

Several writers have employed relatively high doses of penicillin but usually in association with streptomycin, sulfadiazine, or one of the broad-spectrum antimicrobials, so that the effectiveness of the larger doses of penicillin could not be fully evaluated.

Utz and Treger (41) recommended the routine addition of penicillin to sulfadiazine on the basis of three successfully treated cases. The doses of penicillin were relatively low, and further details are not given.

Hager, Migliaccio, and Young (16) isolated an organism from a 16-year-old girl with pleuropulmonary nocardiosis which was susceptible to 0.004 and 0.008 units of penicillin per ml. De-

spite this, the patient did not respond satisfactorily to penicillin given systemically and locally; but she did respond well to 6 to 9 gm. of sulfadiazine per day. Kohn and his co-workers (18) administered 14 million units of penicillin daily to a patient with septicemia due to nocardiosis. The organism was moderately responsive to penicillin, resistant to chloramphenicol, and responsive to chlortetracycline and oxytetracycline. This patient was treated with sodium iodide, sulfadiazine, streptomycin, chlortetracycline, and oxytetracycline and achieved a satisfactory response only with the introduction of the broad-spectrum antimicrobials. Twenty-four million units daily were given to another patient concurrently with probenecid and sulfadiazine, with slow clearing of the chest roentgenogram (42).

The effectiveness of several of the broad-spectrum antimicrobials has been demonstrated *in vitro* (8, 11). Here, too, there is considerable strain variability and lack of parallel between *in vitro* and *in vivo* effects (11). Thus, chlortetracycline, chloramphenicol, and oxytetracycline were shown to be effective *in vitro* against ten strains of *Nocardia asteroides*. However, in mouse protection tests, only chlortetracycline was effective. Large doses of chloramphenicol were needed, and oxytetracycline was found to be of questionable value (8). Sulfadiazine in the same study was highly effective in mouse infection.

Another study (9) showed chlortetracycline to be very effective *in vitro* but not protective for mice. Larsen and co-workers (26) showed variable responsiveness on *in vitro* testing against most of the common broad-spectrum antimicrobials. Four of their seven cases did show *in vitro* inhibition by 25 γ of chloramphenicol, but clinical results were disappointing. This was especially true for streptomycin, erythromycin, and novobiocin. In one patient treated with chloramphenicol for an extended period, the isolated specimen still showed activity of the infection (26). Littman and associates (24) observed resistance to chloramphenicol in amounts greater than 50 γ per ml. Hobby and co-workers (23) demonstrated no inhibition of growth with oxytetracycline in concentrations as high as 298 γ per ml. of medium. There has not been sufficient clinical experience with the broad-spectrum antimicrobials used alone to make valid deductions concerning their effectiveness *in vivo*. Rivera and Perez (25) reported recently on the successful treatment of one case of pulmonary nocardiosis using chloramphenicol following failure with penicillin. There have been failures to respond to broad-spectrum antimicrobials like erythromycin and tetracycline, with subsequent response to sulfadiazine (15, 26).

Several of the sulfones, especially sulfoxone sodium, are known to exhibit protective effects *in vivo* in mice (9) and in human infections (41, 42). The present patient showed no response to an adequate trial of diasone.

Amphotericin B, an antimicrobial produced by the Streptomyces, has been employed in a number of fungous diseases with promising results. However, resistance of Nocardia *in vitro* has been demonstrated (43). The organism isolated from the patient reported here was responsive *in vitro* to 4 γ per ml. No clinical response was noted in this patient following the use of 50 to 75 gm. intravenously daily for six weeks.

Because of the possible biologic relationships of Nocardia and mycobacteria (44), it has been suggested that the antituberculous drugs might be of benefit in nocardial infections (9). The organism in the case reported here was resistant to the agent as well as to *p*-aminosalicylic acid, and clinical trial was without effect. Streptomycin, likewise, has proved disappointing *in vitro* and *in vivo* (8, 11, 47).

The patient reported here illustrates well the therapeutic problems encountered in pulmonary nocardiosis. The organism isolated from sputum and chest wall sinuses at first showed susceptibility *in vitro* only to chlortetracycline and erythromycin; moderate resistance to chloramphenicol, oxytetracycline, and tetracycline; and marked resistance to polymyxin-B, bacitracin, penicillin, and a number of other agents. Subsequent serial cultures showed resistance to all of the above antimicrobials. Chloramphenicol, oxytetracycline, and tetracycline were all clinically ineffective in higher than usual doses, as were sulfoxone sodium and amphotericin B. The patient's improvement was well under way when erythromycin was used so that it is difficult to establish whether it contributed to the therapeutic response. It will be noted, however, that the patient's temperature began to rise following the cessation of penicillin even though she was still receiving erythromycin.

Sulfadiazine, sulfamerazine, sulfisoxazole,

and sulfaethyl-thiadiazole were all used for variable periods. Sulfadiazine and sulfisoxazole had to be discontinued because of fever, leukopenia, and generalized rash. There appeared to be only a temporary response to sulfaethyl-thiadiazole. The patient was able to tolerate sulfadiazine later and continued this drug for one and one-half years without difficulty.

Although this patient was subjected to treatment with a large number of agents simultaneously and successively, the dramatic clinical response was closely related to the initiation of large doses of penicillin intravenously. The drop in temperature, rapid clinical improvement, and occurrence of negative cultures for Nocardia are attributable to the addition of this drug for the following reasons: (*1*) the close temporal relationship of all of the dramatic beneficial effects to the initiation of penicillin intravenously, (*2*) the prior lack of clinical response to several sulfonamides, (*3*) failure of sulfadiazine, restarted two weeks before, to have a demonstrable effect on her course, (*4*) gradual rise of temperature and deterioration of the clinical picture when penicillin was discontinued although sulfadiazine was continued in adequate dosage, (*5*) repeat of response with the reinitiation of penicillin, (*6*) prior failure with the usual dosage of penicillin for extended periods, and (*7*) resistance *in vitro* to 250 γ of sulfadiazine per ml. (*see* table 1).

Another possibility which can be adduced to explain the result achieved in this patient is that of enhancement of the drug action of sulfadiazine with penicillin. McDermott (48) has emphasized the rarity of demonstration of the phenomenon in the human and has indicated its specificity with regard to the drugs involved and the organism. Among the few really acceptable clinical examples, he believes, are the response of the enterococci to penicillin-streptomycin and of the tubercle bacilli to streptomycin-PAS. Of the many combinations of antimicrobial agents employed in the present patient, only penicillin and sulfadiazine were common to the period of improvement. Sulfadiazine alone and penicillin alone, in ordinary dosage, produced inappreciable effects. The response to massive doses of penicillin while on sulfadiazine, the relapse when penicillin was discontinued and the patient was still on sulfadiazine, and the subsequent response with the reintroduction of massive doses of penicillin, all point to enhancement of drug action as a reasonable possibility. McDermott has also pointed out the necessity of testing for potentiation of drug action under the conditions that simulate the *in vivo* environment. The unfortunate loss of the organism in this case precluded such an investigation. The response of *Nocardia asteroides* infections to both sulfadiazine and massive penicillin appears worthy of further investigation from the point of view of enhancement.

The patient had accompanying infection with *Staphylococcus aureus*, which was resistant to all antimicrobials tested, including penicillin. The successful result cannot be attributed to responsiveness of this infection to penicillin, since the cultures remained positive for *Staphylococcus aureus* for a considerable time while the patient improved and while the sputum became negative for Nocardia. Following the second course of penicillin, the patient has remained well for the past three years. Her chest film is virtually normal, the ribs are healed, and the patient leads a normal and active life as wife and mother, completely free of symptoms.

The high solubility and relative lack of toxicity of crystalline penicillin made it possible to achieve concentrations of 1,200 units per ml. in this patient. Through an unfortunate accident, the organism in this case was lost so that its resistance above 100 units per ml. could not be tested *in vitro*. Previous studies, already cited, have shown uniformly high resistance for most strains of Nocardia. Balows (49) tested two additional strains of Nocardia by the tube dilution technique and found resistance to 3,500 units per ml.—the highest dilution tested. The high concentrations achieved in this patient were probably insufficient to inhibit the organism *in vitro*, but this should not militate against a trial of dosages of this order or higher in patients who fail to respond to the sulfonamides and the broad-spectrum antimicrobials alone or in combination.

In the usual susceptibility tests, penicillin is used at concentrations of 0.6 and 6.0 γ, as compared with other antimicrobials at concentrations of 10 and 50 γ. This is because bacteria are the standards of reference. In the case of Nocardia, penicillin and the other antimicrobials should be compared equally. Thus, it was possible to use 30 gm. of penicillin intravenously per day, and in this way peak doses were obtained which were probably of importance in

penetrating the suppurative pulmonary lesions. Because of venous sclerosis and systemic toxic effects, comparable peak concentrations of the tetracyclines could never be reached. Therefore, attainable penicillin concentrations of 1,000 to 2,000 γ or more should be compared with the practically attainable concentrations of the tetracyclines—50 to 100 γ. Penicillin, therefore, in nocardiosis and other infections offers the possibilities of blood concentrations unachievable with any other agent. Its use in 50 to 100 million unit dosages intravenously is worth further application in this and other resistant infections regardless of results of susceptibility typing *in vitro*. The possibility of a synergistic effect of penicillin in high dosage with sulfadiazine was not adequately investigated and is worth further *in vitro* and *in vivo* study.

The treatment of systemic nocardiosis has undoubtedly been influenced favorably by the introduction of the sulfonamides and the broad-spectrum antimicrobials. However, the lack of parallel of the effectiveness of these agents *in vitro* and *in vivo* and the many strain variations in responsiveness to antimicrobial agents present difficult problems. In this infection, as in others, prompt isolation of the organism and precise identification are cornerstones of adequate treatment. *In vitro* susceptibility tests should be obtained, but they must not be too rigidly interpreted in view of the lack of correlation with *in vivo* effectiveness (8, 11, 26, 51). As this case illustrates, a certain measure of empiricism is justifiable and necessary.

The treatment of choice at present is sulfadiazine administered in dosage adequate to achieve blood concentrations of 10 to 12 mg. per 100 ml. Whether or not the sulfonamides should be combined at the outset with chloramphenicol, chlortetracycline, oxytetracycline, or erythromycin is problematic, although Peabody recommends this (21, 22). Frequent repetition of cultural studies is mandatory in following the effectiveness of the regimen selected, and the decision to alter treatment must be constantly evaluated. The result in the patient reported here indicates that, if the sulfonamides, alone or in combination, are ineffective, the use of massive doses of penicillin in addition to sulfadiazine should be considered. Although suggestive, the evidence for the use of penicillin alone is insufficient.

There is no general agreement on the optimal duration of treatment (22). Nocardiosis should be considered analogous to infection with *Mycobacterium tuberculosis*. The present writers are in agreement with others who have suggested treatment for prolonged periods of time, particularly so long as there is roentgenographic or clinical evidence of pulmonary or other involvement. It is well to point out here that this patient was treated for one and one-half years with sulfadiazine and that roentgenographic improvement continued all this while.

Surgical drainage is an important feature facet of the treatment of norcardiosis. There have been a number of reports of the use of surgical resection together with antimicrobials in the treatment of nocardiosis of the central nervous system (51–53) and of the chest (10, 16, 17, 26). The best available treatment today would appear to be a prudent combination of antimicrobials and surgical resection or drainage of abscess. Resection, if done, should be carefully planned, as in tuberculosis, to coincide with maximal clinical improvement on an antimicrobial regimen followed by serial cultures.

Summary

A case of cervical and pulmonary nocardiosis with chest wall involvement and osteomyelitis of the ribs is presented. *Nocardia asteroides* was isolated from sputum, lymph nodes, and chest drainage, and was tested *in vitro* against a large series of antimicrobial agents. The patient failed to respond to the following drugs in various combinations: sulfaethyl-thiadiazole, sulfadiazine, isoniazid, sulfoxone sodium, amphotericin B, and broad-spectrum antimicrobials (including chloramphenicol and tetracycline). There was dramatic response to a regimen consisting of massive doses of penicillin together with probenecid and sulfadiazine. The response to massive doses of penicillin in addition to sulfadiazine was unexpected in view of the known penicillin resistance of most strains of Nocardia. This mode of treatment might be worth consideration in other cases not responding well to sulfadiazine alone or in combination with the broad-spectrum antimicrobials.

The judicious combination and choice of antimicrobials and critically timed surgical resection or drainage of localized lesions would appear to have the potential of altering signifi-

cantly the prognosis of this highly fatal disease. Enhancement of action of sulfadiazine against Nocardia by large doses of penicillin warrants further study.

Sumario

Respuesta de la Nocardiasis Pulmonar al Tratamiento con Dosis Masivas de Penicilina Intravenosamente. Presentación de un Caso Tratado Satisfactoriamente con Cuatro Años de Observación Subsiguiente, Junto con un Repaso de la Literatura

Preséntase un caso de nocardiasis cervical y pulmonar con invasión de la pared torácica y osteomielitis de las costillas. Se aisló la *Nocardia asteroides* del esputo, de los ganglios linfáticos y del líquido del drenaje torácico, ensayándose *in vitro* contra una numerosa serie de medicamentos antimicrobianos y quimioterapéuticos. El enfermo no respondió a las siguientes drogas en varias combinaciones: sulfa-etil-tiadiazoles, sulfadiacina, isoniacida, sulfoxona sódica y anfotericina B, y antimicrobianos de espectro amplio (comprendiendo cloranfenicol y tetraciclina). Hubo una respuesta teatral a un régimen que consistía en dosis masivas de penicilina junto con probenicida y sulfadiacina. La respuesta a dosis masivas de penicilina, unidas a la sulfadiacina, fué inesperada vista la conocida resistencia de la mayoría de las cepas de nocardia a la penicilina. Quizás valga la pena considerar este modo de tratamiento en otros casos que no responden bien a la sulfadiacina sola o combinada con los antimicrobianos de espectro amplio.

Parece que la juiciosa combinación y selección de antimicrobianos y la resección o el drenaje quirúrgicos, ejecutados oportunamente, de las lesiones localizadas, poseen la propiedad potencial de alterar en forma significativa el pronóstico de una enfermedad tan letal. El acrecentamiento del efecto de la sulfadiacina contra la nocardia por dosis masivas de penicilina justifica estudios ulteriores.

Resume

Réponse de la nocardiose pulmonaire au traitement à doses massives de penicilline intraveineuse. Rapport d'un cas traité avec succès, accompagné d'observations suivies pendant quatre ans, et d'une revue de la littérature

Les auteurs présentant un cas de nocardiose cervicale et pulmonaire avec atteinte de la paroi thoracique et ostéomyélite costale. On isola *Nocardia asteroides* de l'expectoration, des ganglions lymphatiques et du drainage thoracique, et on l'étudia *in vitro*, avec une large série d'agents antimicrobiens et chimiothérapeutiques. Le malade ne put répondre aux médicaments suivants associés de façon variée: sulfa-éthyl-thiadiazole, sulfadiazine, isoniaside, sulfoxone de soude, et amphotéricine B, et des antimicrobiens à large spectre (y compris chloramphenicol et tétracycline). Il y eut une réponse saisissante à un mode consistant en des doses massives de penicilline ajoutée aux sulfadiazines et probenecide. La réponse à des doses massives de penicilline ajoutée à des sulfadiazines fut surprenante, vu que l'on sait que la plupart des souches de Nocardia sont résistantes à la penicilline. Ce mode de traitement peut mériter de la considération dans d'autres cas ne répondant pas bien aux sulfadiazines seules ou associées à des antimicrobiens à large spectre.

L'association judicieuse et le choix d'antimicrobiens, et la résection chirurgicale au moment critique, ou le drainage des lésions localisées sembleraient pouvoir changer notablement le pronostic de cette maladie hautement fatale. Le réenforcement de l'action des sulfadiazines contre les Nocardia par des grosses doses de penicilline mérite des études plus poussées.

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IDIOPATHIC PULMONARY HEMOSIDEROSIS[1,2]

Report of a Case from Japan

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INTRODUCTION

The diagnosis of idiopathic pulmonary hemosiderosis was made recently in a Japanese child referred to the Clinic because of an abnormal chest roentgenogram. A search of the recent Japanese medical literature has failed to produce a report of idiopathic pulmonary hemosiderosis although the number of cases reported from Europe and the United States is increasing (1). The pathologic features of this disease were well described first by Ceelen in 1931 (2), but it was not until ten years later that Waldenstrom (3) reported the first antemortem diagnosis of this condition. The main clinical features of this syndrome are anemia, cough, hemoptysis, dyspnea, and abnormal chest roentgenographic findings, usually occurring in a child or young adult. The natural history of this disease is one of remission and exacerbation, and it usually terminates fatally. The diagnosis is confirmed by demonstrating hemosiderin-laden macrophages in the sputum, fasting gastric contents, or in the lung parenchyma, by means of needle aspiration (4).

CASE REPORT

S.H., a 7-year-old Japanese female, was referred to the Atomic Bomb Casualty Commission Clinic in Hiroshima because of anemia and an abnormal chest roentgenogram. Her chief complaint was listlessness. The child was in good health until the age of four years and nine months when she had an illness characterized by pallor, dyspnea, and malaise. No cyanosis or hemoptysis was observed. She was anemic and was noted to have a positive tuberculin skin reaction and an abnormal chest roentgenogram. Because of these findings she was treated with para-aminosalicylic acid (PAS) and streptomycin for six months. The child also received three blood transfusions during this period. A follow-up chest film was reported as normal.

The patient was well until February, 1960, when she developed hemoptysis and fever during a family and neighborhood epidemic of an influenza-like illness. Her illness lingered and pallor developed. She was found to be anemic, and 500 ml. of whole blood were given. Her chest film was abnormal at this time, and on March 16, 1960, she was seen in the Atomic Bomb Casualty Commission Clinic for diagnostic evaluation.

She was the product of a normal delivery and had weighed 2.65 kg. at birth. No abnormalities were noted at that time. Her mother had had some kidney disorder during pregnancy. The child was breast-fed, and both nutrition and development were considered normal during infancy. In early childhood her appetite was poor. The primary constituents of her diet were boiled rice, seaweed, and eggs occasionally. At six years of age she had measles and mumps. Her academic record has been below average.

A paternal uncle had died of pulmonary tuberculosis prior to the patient's birth.

On physical examination the child appeared thin but not acutely ill. The oral temperature was 37.7°C.; the pulse was 130 per minute. Respirations were 22 per minute and regular, and the blood pressure was 90 systolic, 56 diastolic in mm. of mercury. The patient was pale, but there was no icterus or cyanosis. Firm, easily movable, nontender pea-sized lymph nodes were palpable in the axillae, inguinal areas, and the neck. Examination of the chest revealed that the left lower thorax was more prominent than the right. Respiratory excursions were equal. Harsh breath sounds were heard over the left upper lung field, but the rest of the pulmonary examination was normal. A grade I blowing apical systolic murmur was heard, but it disappeared when the patient assumed the sitting position. The liver edge was palpable 2 fingerbreadths below the right costal margin in the midclavicular line, but it was not tender. The upper border of liver dullness was within normal limits. The spleen was not palpable. The rectal examination was normal, and the remainder of the physical examination was within normal limits.

The laboratory results revealed a hemoglobin of 7.3 gm. per 100 ml. and a hematocrit of 29.0 per

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[2] This work was performed while Dr. Rudnick was assigned to the Atomic Bomb Casualty Commission, Hiroshima-Nagasaki, Japan, a research agency of the United States National Academy of Sciences, National Research Council, under a grant from the U. S. Atomic Energy Commission, administered in cooperation with the Japanese National Institute of Health of the Ministry of Health & Welfare.

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FIG. 1. Roentgenogram obtained on March 16, 1960, showing diffuse opacification of right lung field and mottled left lung field densities. Although the film was made in incomplete inspiration, the changes are thought to be significant.

cent. The reticulocytes were 29.2 per cent. There was a positive guaiac reaction in the stool. Other preliminary tests were normal with the exception of the routine chest roentgenogram (figure 1), which showed consolidation of the right middle lobe, probable atelectasis of the anterior portion of the right lower lobe, and parenchymal infiltrates in the left upper and lower lobes. The patient was admitted five days later to the diagnostic ward for further study.

Additional laboratory studies showed the erythrocyte indices to be hypochromic and microcytic with a reticulocyte count of 20.2 per cent. The erythrocyte sedimentation rate (Wintrobe) was 12 mm. in one hour and the platelet count was 152,500 per cu. mm. The total leukocyte count was 6,650 per cu. mm. with 82.0 per cent neutrophils, 14.0 per cent lymphocytes, 1.0 per cent monocytes, 1.5 per cent eosinophils, and 1.0 per cent basophils. The smear revealed moderate anisocytosis, basophilic stippling, and hypochromasia. The bleeding, clotting,[4] and prothrombin times were normal. Sternal bone marrow was interpreted as moderate late erythroid hyperplasia. Erythrocyte osmotic fragility was normal. (Hemolysis began at 0.46 per cent NaCl and was complete at 0.38 per cent.) Mechanical fragility of erythrocytes was normal (3.8 per cent). The serum iron was 7 γ per 100 ml. with an unsaturated iron-binding capacity of 286 γ per 100 ml. The nonprotein nitrogen and fasting blood sugar determinations were normal. The total serum protein was 6.5 gm. per 100 ml. The albumin was 4.3 gm. per 100 ml., and the globulin was 2.2 gm. per 100 ml. Total bilirubin was 5.91 mg. per 100 ml., and the direct reacting fraction was 1.05 mg. per 100 ml. Bromsulphalein® dye retention was 1.5 per cent after forty-five minutes. The alkaline phosphatase was 8.97 Shinowara-Jones units. The thymol turbidity and cephalin flocculation tests were normal, and the serum glutamic oxaloacetic transaminase was 40 units.

The chest film upon admission showed a marked interval change (figure 2). Complete resolution of the processes in the right middle and lower lobes had occurred. The densities in the left upper and lower lobes remained. On the second hospital day the patient's temperature was 38°C. She was noted to be icteric, and the tip of the spleen was palpable but nontender. She had an episode of hemoptysis which was productive of bright red blood mixed with white sputum. During her three weeks' stay in the hospital she had a total of four similar episodes of hemoptysis, but frequent examinations of the chest were unrevealing. Her jaundice decreased gradually during her hospital stay. One week after admission the spleen was no longer palpable. The temperature gradually returned to normal after remaining slightly elevated for two weeks. The chest roentgenogram, one week after admission, showed mottled densities in the left

[4] Lee and White.

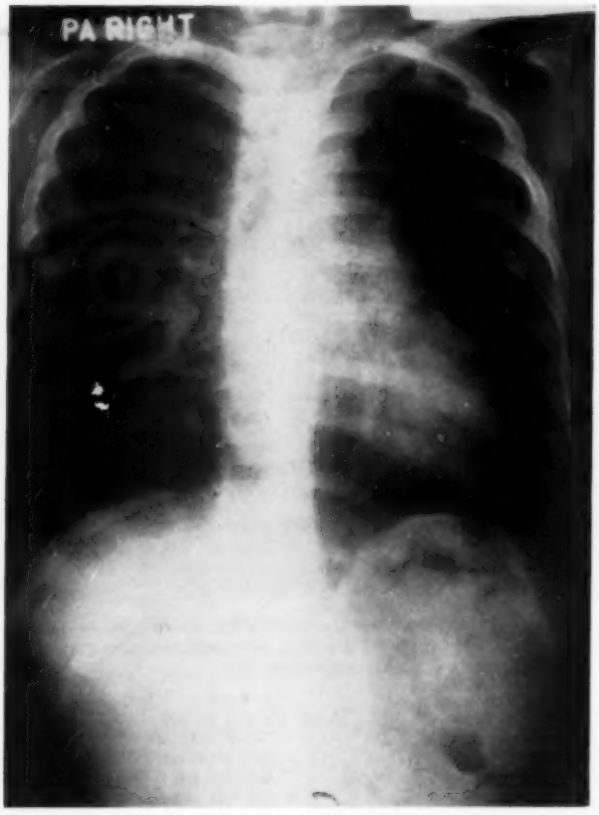

FIG. 2. Roentgenogram obtained March 22, 1960, showing resolution of right lung field opacification.

lower lobe. The similar densities in the left apical region which had been noted one week previously were visualized only faintly. One week after admission the total bilirubin was 1.87 mg. per 100 ml., the hemoglobin was virtually unchanged, but the reticulocyte count was 8.8 per cent. Urinary urobilinogen which had been elevated upon admission returned to normal after ten days.

Pertinent negative laboratory results included the Coombs' test, the heterophil agglutination test, and the cold agglutination test. The routine sputum culture revealed a mixed flora plus *Candida albicans*. Numerous sputum collections and examinations of gastric washings for acid-fast bacilli were negative. The intermediate-strength PPD skin test was positive. Numerous stool examinations revealed Enterobius and *Trichocephalus ova*, and on one occasion there was a strong positive guaiac reaction. Because of this finding, an upper gastrointestinal series was performed, but this was interpreted as normal. The electrocardiogram revealed high voltage of the QRS complex.

The patient's history, along with the episodes of hemoptysis and marked interval change of the chest film, suggested the diagnosis of idiopathic pulmonary hemosiderosis. Intracellular hemosiderin was demonstrated in macrophages recovered from both the sputum and fasting specimens of gastric washings.

At the time of discharge, although the patient was feeling well and was no longer jaundiced, the hematocrit was 23.0 per cent and the hemoglobin 6.2 gm. per 100 ml. The reticulocyte count was 7.8 per cent. The patient was started on a program of oral ferrous sulfate therapy, 0.6 gm. per day, and was discharged to her home.

One month after discharge from the ward, the patient was seen and found to be well. The physical examination was within normal limits with the exception of a palpable liver, again 3 cm. below the right costal margin. She was not icteric. The hemoglobin was 12.5 gm. per 100 ml. and the hematocrit was 41.0 per cent. Reticulocytes were 4.3 per cent. The total bilirubin was 1.45 mg. per 100

ml., and the direct reacting fraction was 0.07 mg. per 100 ml. The patient had discontinued oral iron therapy one week prior to her visit, and the serum iron concentration was 57 γ per 100 ml. The unsaturated iron-binding capacity was 190 γ per 100 ml. A chest film revealed a decrease in the parenchymal densities in the left upper and lower lobes. There was very faint opacification in the region of the right midlung field.

Again, the patient was discharged home on a therapeutic program similar to the previous one. She was seen two months later, at which time she reported no episodes of cough, icterus, or hemoptysis. She had failed to gain weight since her hospital admission. The liver edge was palpable, and at this examination the splenic tip was palpable and nontender. The hemoglobin was 10.8 gm. per 100 ml. and the hematocrit was 33.0 per cent. Reticulocytes were 8.1 per cent. Urinalysis was normal. The total bilirubin was 2.25 mg. per 100 ml. and the direct reacting fraction was 0.24 mg. per 100 ml. Again the patient had discontinued her iron therapy one week prior to her visit, and the serum iron was 25 γ per 100 ml. The unsaturated iron-binding capacity was 270 γ per 100 ml. The patient's chest roentgenogram revealed no interval change in the two-month period. She was discharged and advised to continue oral ferrous sulfate therapy and to return to the clinic if she developed symptoms of her disease.

The patient returned to the clinic ten weeks later, and her family reported an episode of pallor, jaundice, dyspnea on exertion, nausea, and vomiting, the absence of fever and hemoptysis, which occurred one month prior to her visit. She was not examined at that time, but her illness was said to have lasted some ten days. She had discontinued her iron therapy after this brief illness. On physical examination the liver was palpable 2 cm. below the right costal margin. The spleen was not palpable. Examination of the chest was within normal limits. Again she had failed to gain weight.

Laboratory studies revealed a hemoglobin of 11.2 gm. per 100 ml. and a hematocrit of 38.0 per cent. The reticulocyte count was 2.4 per cent. The serum iron was 10 γ per 100 ml., with an unsaturated iron-binding capacity of 369 γ per 100 ml. The stool and urine examinations were within normal limits. The total bilirubin was 0.83 mg. per 100 ml. and the direct reacting fraction was 0.03 mg. per 100 ml. The chest roentgenogram revealed the previously described densities in the left lower and upper lobes. Faint opacification of the right midlung field again was noted along with pleural thickening of the anterior portion of the right leaf of the diaphragm. An electrocardiogram was within normal limits.

The patient was discharged on the same therapeutic regimen as before and advised to return to the clinic at quarterly intervals for examination. She returned seven weeks later complaining of cough, fever, dyspnea, tachycardia, and malaise of four days' duration. Her grandmother said the child was icteric during that period. She was pale and had slightly icteric conjunctivae. The oral temperature was 38°C, the pulse 102 per minute, and she was tachypneic, but there was no cyanosis. Rales were audible over the right middle lung field posteriorly. The liver was palpable 3 cm. below the right costal margin. The hemoglobin was 8.7 gm. per 100 ml. and the reticulocyte count was 9.9 per cent. Urinary urobilinogen was elevated, and the total bilirubin was 3.98 mg. per 100 ml. with a direct fraction of 0.24 mg. per 100 ml. The serum iron was 29 γ per 100 ml., and the unsaturated iron-binding capacity was 223 γ per 100 ml. The chest film revealed an increase in the extent of the previously described parenchymal densities delineating the aerated bronchial structures and rendering a lack of definition about the right cardiac border (figure 3). Hospitalization was advised, but the patient's family wanted to keep her at home.

Discussion

There are many features of this illness which indicate that the patient has idiopathic pulmonary hemosiderosis. The most important of these is the demonstration of intracellular hemosiderin in the fasting gastric washings and sputum specimens. Combined with anemia, an abnormal chest roentgenogram, episodes of hemoptysis and jaundice, and the absence of clinically evident heart disease, the over-all picture is characteristic. It is difficult to date the precise onset of this patient's disease. The episode of anemia in association with pulmonary abnormalities shown roentgenographically when the patient was four years old may have represented pulmonary tuberculosis. Other features in favor of this are the positive tuberculin skin reaction and the change in the roentgenographic findings in the lungs after the course of antituberculous chemotherapy. No bacteriologic studies or tests for hemosiderin were performed at that time. However, in restrospect, it is believed that this was the first episode of intra-alveolar bleeding. The patient's most recent episodes again represented mild bouts of intrapulmonary hemorrhage.

Until recently, idiopathic pulmonary hemosiderosis was thought to be a disease virtually limited to children and with a uniformly bad prognosis. However, as more cases have been reported (1), adults are seen to be afflicted (5) with this syndrome, and prolonged (6) and suspected complete (7) remissions have been described. The age of onset is usually in early childhood, but a few of the adult cases have

FIG. 3. Postero-anterior roentgenogram obtained October 31, 1960, showing increase in parenchymal densities in left upper and right lower lobes. Note the delineation of bronchial markings in right lower lobe.

been described with onsets after thirty years of age (6). The sex incidence changes from the childhood to the adult form. In the younger patients, females have the disease more commonly than males; whereas, in adults, the ratio is reversed. A recent review has documented 37 cases with the onset at the age of sixteen or older (5).

Classically, the acute attack consists of dyspnea, cough, hemoptysis, cyanosis, tachycardia, fever, and pallor. These are the effects of the acute intra-alveolar hemorrhage. After a few days icterus may appear and, within a week or two, the episode will be terminated. The lack of physical signs on auscultation of the chest is impressive in view of the symptoms and abnormal chest roentgenogram. The chest film may become progressively clearer or the infiltrates may remain stationary. Marked anemia and reticulocytosis and sometimes leukocytosis and eosinophilia are noted (8). If the acute episode progresses, acute cor pulmonale may develop, and death will ensue. Hepatosplenomegaly, clubbing of the fingers and toes, and hematemesis from swallowed blood may be observed. The subacute episodes may be difficult to detect since the symptoms are limited to cough, mild anemia, dyspnea, and minimal hemoptysis.

Bronson (5) recently has reviewed the roentgenographic findings in this disease. Small nodular infiltrates frequently are bilateral and predominantly in the perihilar and lower lung field areas. However, all parts of the lung are susceptible, and pleural effusion has also been described in an adult patient. The infiltrates may vary in size from a few millimeters to 3 cm. in diameter and sometimes will have radiolucent

centers. The large areas of homogeneous densities seen during acute attacks often clear and sometimes are replaced by a pattern quite similar to interstitial fibrosis or granulomatosis. In fact, the roentgenographic picture is often confused with hemosiderosis secondary to sustained pulmonary hypertension, as in mitral stenosis, miliary tuberculosis, other granulomatoses, or carcinomatosis. Multiple pulmonary hemangiomata with recurrent bleeding may cause similar roentgenographic and clinical findings (9).

The etiology of the anemia has been puzzling because of the coexistent features of iron deficiency and hemolysis. Recently, Apt and associates (10), by using radioisotopic techniques, have demonstrated that the anemia is caused by blood loss into the alveoli, and for still unknown reasons the iron is sequestered in the lungs. Apparently the amount of blood destroyed in the lungs is sufficient to account for the observed hyperbilirubinemia. Unlike a hemolytic anemia, the erythrocyte survival is normal when corrected for blood loss, the serum iron is low, and most of the sequestered iron is unavailable for reutilization in hemoglobin synthesis. These excellent studies also demonstrated that during remission, erythropoiesis and erythrocyte survival were normal.

As the pulmonary lesion becomes more extensive, anoxemia develops and, because of embarrassed oxygen diffusion, compensatory erythrocytosis may be observed. Thus, a normal hemoglobin in a late stage of the disease is seen occasionally.

Pathologic findings are limited to the lungs, mediastinal lymph nodes, and occasionally the myocardium. The lungs are heavy, firm, and dark red in color, and there is enlargement of the tracheobronchial nodes. There may be right ventricular hypertrophy, and in four reported cases there has been an associated myocarditis (11). The alveoli are crowded with erythrocytes and hemosiderin-laden macrophages. Hemosiderin granules may be lying free in the alveoli as well as in the tracheobronchial nodes. There is a markedly increased amount of hydrolyzable iron in the lungs (12). Hemosiderin is hardly ever found in the liver, spleen, or other lymph nodes. The pulmonary interstices are thickened and contain hemosiderin, as do the elastic fibers of the alveolar septa and smaller blood vessels. Since the elastic fibers are frequently fragmented and deficient in number, in the past some writers (3, 8) have believed that this is the primary lesion of the disease. However, there are well documented reports (13) that show normal elastic fibers in the presence of acute disease. Now it is considered a result rather than a cause. There may be a diffuse interstitial pulmonary fibrosis as a result of long-standing disease. Recently, an acute fatal nephritis has been observed in a few young adults with the disease (14).

Concepts are plentiful, but the true pathogenesis has yet to be delineated. Steiner (15) has championed an autoimmune mechanism, the lungs being the "shock" organ. He has had inconsistent results using splenectomy in treatment of the disease. In 1939, Anspach (16) noted necrotizing arteritis of the lungs at the autopsy of one patient with the syndrome. The occasional therapeutic response to adrenal steroids and corticotropin (17) also supports the immunologic theory. Lendrum (18) believes that diapedesis of erythrocytes at the junction of pulmonary artery radicals and the bronchial vasculature is the source of intra-alveolar bleeding. Some writers postulate a defective vasomotor control of the pulmonary vascular bed causing episodes of transient pulmonary hypertension (1), whereas others think that a change in the permeability of the capillary bed is responsible (5). Newer theories are those of Propst (19), who has demonstrated excessive acid mucopolysaccharide in the elastic fibers, thus weakening them and causing bleeding. It might be speculated that it is this increased mucopolysaccharide which binds the iron and sequesters it in the lungs. Herzog (20) has demonstrated proliferation of pulmonary capillary argyrophil fibers, and he considers this to be the primary lesion of idiopathic pulmonary hemosiderosis.

As may be expected in diseases which are poorly understood, the treatment for this syndrome leaves a great deal to be desired. Some newer modes of therapy have been mentioned, but basically the treatment consists of supportive measures for the anemia, hemoptysis, and episodes of pulmonary and cardiac decompensation.

Summary

A case of idiopathic pulmonary hemosiderosis in a Japanese child has been investigated and described. The diagnosis was confirmed by the

demonstration of hemosiderin in phagocytes of the sputum and gastric washings. The clinical course, pathology, roentgenographic findings, and concepts of pathogenesis have been discussed. It is unlikely that the lack of case reports in the literature represents the true incidence of the disease in Japan.

Sumario

Hemosiderosis Pulmonar Idiopática. Presentación de un Caso del Japón

Se ha investigado y descrito un caso de hemosiderosis pulmonar idiopática en un niño japonés. El diagnóstico quedó confirmado con el hallazgo de hemosiderina en los fagocitos del esputo y de los lavados gástricos. Se discuten la evolución clínica, histopatología, hallazgos radiográficos y conceptos de la patogenia. Es improbable que la falta de historias clínicas en la literatura represente la verdadera incidencia de la enfermedad en el Japón.

Resume

Hémosidérose pulmonaire idiopathique. Rapport d'un cas du Japon

Les auteurs ont étudié et décrit un cas d'hémosidérose pulmonaire idiopathique chez un enfant japonais. Le diagnostic fut confirmé par la mise en évidence d'hémosidérine dans les phagocytes de l'expectoration et dans les lavages gastriques. L'évolution clinique, la pathologie, les données radiographiques et les concepts pathogèniques sont discutés. Il est invraisemblable que le manque de rapports de ce cas dans la littérature représente la vraie fréquence de la maladie au Japon.

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Editorial

Measurement of the Tuberculosis–Alcoholism Problem in Massachusetts and Steps to Combat It

Across the nation, medicine has dealt increasingly devastating blows to tuberculosis. There is scarcely a state that does not show the sharp decreases in morbidity and death rates that have become the rule in a relatively short time. Nevertheless, this disease has by no means vanished from the American scene and, even in those communities which enjoy the lowest prevalence figures, the downward trend cannot be said to have reached the ultimate minimum toward which present efforts are directed. There is much to challenge these efforts, and it is the purpose of this paper to describe one of the most vigorous pockets of resistance and to show what at least one state is doing about it.

We refer, of course, to the special problem posed by the tuberculous patient who is also an alcoholic. It is a matter that plagues us in and outside of sanatoriums and stands out as one characteristic of a considerable portion of tuberculous patients whose successful treatment is consistently in doubt and whose presence in the community represents a potential hazard to the health of others. Apart from the medical aspects of the problem, the social and economic burdens imposed on the community are very great indeed.

Alcoholism among tuberculous patients is not a new development; it is only with the advances made in the conquest of tuberculosis that it now stands revealed as a major obstacle to the adequate control of tuberculosis. As these findings have developed, more attention has been focused on efforts which are designed to mitigate the negative influence of alcoholism on the usual processes involved in tuberculosis control. In the development of techniques and devices for coping with this "new" phenomenon, medicine now stands where it stood thirty years ago in its crusade against tuberculosis. At that time, both incidence and death rate were discouragingly high; but tenacity and imagination in the laboratory, the sanatorium, and in the area of public education have paid off handsomely. On the other hand, the tools for the treatment of alcoholism, whether with or without tuberculosis, have only recently been forged, and it remains for the passage of time to reveal whether they are crude instruments or whether they are already sufficiently refined for the purpose at hand. We do know that in alcoholism we are not dealing with the "germ" theory or the direct passage of defective genes. Whatever else is to be done from a strictly medical point of view, the tasks of treatment and prevention are multiplex in nature, requiring attention to the social, psychologic, and economic milieux which have been characteristic of the patient's life situation.

When we examined the general literature at the outset of our study, it showed that concern over tuberculosis-alcoholism is not new. It revealed also that much of the early comment was either highly impressionistic or based on observations which might not bear close scientific scrutiny. There was wide variation in reported results; consequently, it became clear that, through our own efforts, we should determine the facts about the problem as it exists in Massachusetts. A few comments on the literature examined may make clearer the necessity for this:

A study made in France in 1864 concluded that tuberculosis was less frequent among alcoholics than among "sober patients." Another study, in 1897, arrived at the opposite generalization: tuberculosis was found to be *more* frequent among alcoholics than among sober patients. There was nothing to indicate the prevalence of alcoholism among tuberculous patients as a group.[1]

In Sweden, in 1908, an analysis of statistics dealing with tuberculosis and alcoholism showed that the incidence of alcoholism among tuberculous patients was "very low." No definition of "low" was suggested.[1]

A report on all male admissions for alcoholic psychosis made in 1948 for mental hospitals in New York State revealed that pulmonary tuberculosis was present in 4.1 per cent.[2]

Several reports on populations outside of Massachusetts and geographically remote from one another showed a great range of difference in the findings regarding the relation between the two diseases and did not negate a correlation between them. Everywhere in recent reports, in which the disease entities are considered together, they appear many times more frequently than might be expected when viewed separately. In Massachusetts, for example, tuberculous patients admitted to state, county, and municipal sanatoriums between June 1, 1958, and February 1, 1959, showed an alcoholism prevalence of more than 28 per cent. In the nontuberculous, alcoholism is conserva-

[1] Golder, G.: Conn Rev Alcoholism, 1952, *3*, No. 5.

[2] Malzberg, B.: Quart J Studies on Alcohol, 1949, *10*, 461.

tively estimated at only 5.3 per cent. Conversely, a study of 1,468 consecutive alcoholic commitments to the state correctional institution at Bridgewater showed a pulmonary tuberculosis rate of 5.5 per cent. This is sixteen times the 0.35 rate of tuberculosis in the general population,[2] as determined by community roentgenographic surveys. These statements are indicative of the increasing concern over the two illnesses in combination and the increasing quality of the data which suggest, more than strongly, that they bear some relationship to one another, notwithstanding the fact that the nature of their relationship is as yet unclear.

In addition to collecting and coding the voluminous professional literature pertaining to this problem, the Division of Alcoholism of the State Department of Public Health has made abstracts of more than forty articles, some of which have been translated into English from several European languages.

The next logical step was to make a nation-wide inquiry, in the form of a questionnaire, on the supposition that the replies would provide a suitable basis for constructive effort. Accordingly, under the joint auspices of the State Health Department's Division of Sanatoria and Tuberculosis Control and Division of Alcoholism, a questionnaire was mailed to sixty of the largest sanatoriums in the United States. The questions sought to discover the extent of the problem in other localities and whether effective measures had been devised to cope with it. The answers received helped to verify that our concern was realistic and that there were sound economic and medical reasons for augmenting the modest program that was already under way. It was also revealed that no other public health agency was contemplating activity similar in scope to that which we envisioned. On the basis of these findings, the next step taken was to make a study of alcoholic and nonalcoholic patients in one of our local institutions.

With the cooperation of the Superintendent,[4] a study was conducted in a nearby county sanatorium. Funds were provided by the Division of Tuberculosis Control, and Dr. Albert D. Ullman, Chairman of the Department of Sociology at Tufts University, accepted the responsibility for, and leadership of, the formal investigation which was conducted during the summer of 1958. Valuable clues emerged to aid us in our quest for increasingly sophisticated data. One of the results was the development of a tentative "profile" of the male alcoholic patient which stood in contrast to a control group of nonalcoholic patients. The main features of this profile were as follows[5]:

The subjects had been alcoholics for an average of eighteen years prior to contracting tuberculosis.

They were characterized by a high degree of social disorganization and instability in such areas as marriage, occupation, employment, and residence. An average of ten arrests per patient were recorded, mainly on charges involving drunkenness.

While none denied his alcoholism, 25 per cent denied the diagnosis of tuberculosis. (In passing, it is interesting to note that the same 25 per cent said they saw no relation between the two illnesses.)

About one half of the alcoholic group had had previous admissions to sanatoriums, and more than three fourths of these had left hospitals against medical advice.

The alcoholic patients were less likely to have completed high school than were the nonalcoholics; and they were more likely to have been born in Massachusetts of parents who were born in the United States.

Although these and other findings were not far reaching, the results were appropriate to the size and intent of the project. The study provided us with information where none had existed before, and it formed (as suggested elsewhere) a basis for the beginning of what may be called the "action sequel." Recommendations growing out of this and other studies collated with advice from such well-established agencies as the Massachusetts Tuberculosis and Health League, Inc. and its local affiliates were implemented in a number of ways, as the remainder of this report shows.

Space limitations preclude a description of the coordinating efforts undertaken through various agencies, both public and voluntary, to initiate the action programs dictated by the research activity. Suffice it to say that, as more and more responsible persons became involved in the planning, a momentum of community organization was created and it attained considerable effectiveness. Only the opening chapters of this story can be told at this point because the events described below have only recently come about. They are beginnings, but such promising beginnings that we are tempted to predict their fruition into highly viable advances across a new public health frontier.

An important concrete step has been taken by Dr. David Sherman, Superintendent of Boston Sanatorium. He has made a special provision for

[2] Massachusetts Department of Public Health, Division of Tuberculosis Control: Massachusetts Tuberculosis Facts and Figures for 1956 and 1957.

[4] Dr. Howard M. Payne, Middlesex County Sanatorium, Waltham, Massachusetts.

[5] Ullman, A. D., and Urbanowicz, M. R.: Report on a study of tuberculous alcoholics in a county sanatorium, Massachusetts Department of Public Health, September, 1958.

the care and treatment of alcoholic patients by establishing a rehabilitation center and "halfway house" on the grounds of the Sanatorium. The purpose of this program is to help those whose tuberculosis has become inactive and who are medically ready for discharge to their respective communities. Medical readiness in such patients is only a part of their problem, since alcoholism remains as a serious hazard. Since the majority of the persons who take advantage of this type of experience are middle-aged males without family or other close personal ties, such a transition process is deemed crucial for positive rehabilitative results. Provision has been made for recreation, case-work services, employment counseling, and psychiatric consultation, in addition to the more customary type of medical supervision. The last phase of the treatment sequence is the patient's "graduation" to permanent living quarters away from the institution.

During the summer of 1958, Dr. W. H. Weidman, the Director of the Division of Tuberculosis Control, developed a registry of tuberculous alcoholics among the patients admitted to tuberculosis sanatoriums throughout the state. The question of whether the patient is an alcoholic is determined during the routine examination procedure at the time of the patient's admission to the sanatorium. A common definition following that recommended by the World Health Organization is used by each physician, and it is presumed that this factor contributes to a higher degree of accuracy and uniformity than would obtain if random, impressionistic diagnoses were made. As a result, there is, for the first time in the history of this state's health program, a regularized flow of information capable of providing us with data which can be used for planning and the development of treatment techniques.

We cannot leave this discussion without a word about another problem which has come to be associated with that of the alcoholic, namely, those persons with tuberculosis who either will not or cannot care for themselves outside of sanatoriums and who refuse hospitalization. In Massachusetts, the recalcitrant patient is now legally committable to a "security treatment unit," but this action is not taken until a series of "qualifying" conditions have been met and satisfied. These conditions, in effect, leave neither the patient nor the agencies of enforcement any alternative except compulsory commitment. A unit of this kind was established at the Rutland State Sanatorium in 1958, and new light has been shed on the over-all problem since that time. To date, 102 persons have been referred for investigation and, while not all were committable, it is interesting to note that many more than 50 per cent were alcoholics. Of those who have been committed nearly *all* were alcoholics. This experience forces the conclusion that alcoholism is inevitably linked with recalcitrancy.

When information began to accumulate as a result of the first measures taken to implement research findings, it became obvious that the problem had many ramifications and was important enough to require the full-time attention of at least one professional worker to whom a variety of responsibilities could be assigned. In the main, these duties would be in the field of research, but would require also that the individual relate himself to specific institutions in order to understand the practical, day-to-day problems faced by staff and patients alike. In addition, his activity should lay a foundation for specialized research programs geared to the treatment and preventive aspects of the problem. With these ideas in mind, Dr. Weidman, in February, 1959, created the position of epidemiologist and added this new member to his staff.

As one indication of the readiness of our institutions for such a development, the staffs of several have evinced an active interest in the epidemiologist's program by inviting him to conduct discussion groups along the general lines of mental health consultation to help them understand more about alcoholism and the management of everyday disciplinary problems on the wards. At the present time, the epidemiologist holds regular meetings with both staff and groups of patients in four different sanatoriums. This work attests clearly to the existence of a recognized need long before this aspect of the program was created.

Early in the history of our action program, the problem of introducing meaningful, pervasive education relative to this special field was recognized to be of great importance. A guiding principle was developed out of many interagency discussions and has proved to be sound. The principle is simply an attempt to meet the needs which laymen and professionals *recognize* as their needs and in terms of what they believe will help them to function more effectively in dealing with the tuberculous alcoholics they encounter in the course of their work. Observing this principle, in its most practical sense, the following programs have been introduced:

Specialized intensive training for key workers in both public and voluntary agencies at the Summer School of Alcohol Studies conducted annually by Yale University. With funds supplied by the Department of Public Health, ten persons have received this training during the past two summers, and more will be similarly trained in the future. The list includes social workers, rehabilitation counselors, and public health nurses, each of whom, by virtue of his professional commitment,

is in a position to make immediate contact with a considerable proportion of the alcoholic patients in and outside the sanatoriums of this state.

Public understanding is sought through the various media of mass communication. In addition to regular newspaper releases, the Department of Public Health, through its divisions of Health Information, Alcoholism, and Tuberculosis Control, and the Massachusetts Tuberculosis and Health League, has been active in providing many group meetings with exhibits, motion pictures, and specialized literature on the subject; and more than a dozen radio programs have been broadcast to a wide audience during the past year.

The Division of Alcoholism has been particularly active in the development of in-service training programs for groups of "front-line" workers without whose functioning other elements of the educational program would be largely pointless. These are the public health nurses, visiting nurses, police officials, local health and welfare officers, social workers, clergymen, nurses and physicians in general and mental hospitals, and the like. These workers meet the problem head-on in contexts which range from the urgent, "crisis" needs of individuals and families to the long-term follow-up care of the tuberculous patient who is discharged from the sanatorium. Clearly, educational programs for this important corps of workers take precedence over all other forms of supportive activity. The meetings have been tailored to meet the time schedules and stated needs of each group. They have been as brief as a two-hour afternoon session, as long as three consecutive days.

* * *

The tasks that lie ahead for this beginning program are fraught with many baffling problems, not the least of which is that of achieving a more detailed understanding of the disease complex per se. We know that the causal element in alcoholism, apart from its significance for tuberculous patients, is not unitary in nature and that its contributory agents must be opposed by treatment techniques derived from the social sciences as well as from medicine. We are convinced that research activity should be incorporated into treatment plans whenever possible, because there still is not enough verified knowledge extant of the maximal potential for success in this area of study.

More specifically, since the locus of the patient's treatment will be the sanatorium, it is here that attention to the alcoholic aspect can be initiated. Ideally, the treatment process would involve participation by the entire staff functioning under the leadership of a practitioner oriented in the field of psychosomatic medicine and skilled in group consultation techniques. This is to say that a number of methods would be developed which are based on the recognition that each patient is a great deal more than his disease; that he is, in fact, a physiologic, cultural, and psychologic entity identical to no other human being, and that the interplay of these elements has had some bearing on the way in which he became ill, the meaning to him of his plight, and the way he will make use of help in overcoming it.

In addition to drugs, bed rest, et cetera, the general atmosphere of the sanatorium should be therapeutic in nature at all levels of activity that impinge upon the patient's life and awareness. Nothing could be clearer than the fact that bed rest is not restful if the patient is under tension from extreme anger or fear, and that surgery cannot serve its full purpose unless the patient is profoundly accepting of it. Treatment of any sort must be administered under circumstances which include understanding *by* the patient as well as *of* him if he is to be prevented from mobilizing his defensive resources against his own optimal recovery. Social work, medicine, and rehabilitation are not isolated areas and, therefore, their practitioners must be prepared to respect one another and to work in close coordination for the purpose of anticipating and mitigating the ravages of stress, whether environmental or emotional. This may often mean helping the patient to accept matters which are beyond his immediate control, or it may indicate the necessity for psychologic support and the development of insights relating to the parts played by himself and others in bringing about some aspect of his present difficulties.

It is not our intention to suggest that none of these considerations are observed or practiced in any of our institutions or that psychological understanding of illness and recovery is a new idea. What we wish to emphasize is that, for the tuberculous, there is no such program operating on a broad conceptual basis; that is, instituted as administrative policy and integrated throughout the sanatorium. Rudimentary efforts have been made along these lines in isolated instances. As reported elsewhere in this statement, the Halfway House at Boston Sanatorium and the group discussions with nurses and patients at Rutland State Sanatorium and at Middlesex County Sanatorium are innovations of recent date, highly exploratory and tentative. If this type of program is to continue and to be extended to sanatoriums throughout the state, it is imperative that it be encouraged by those with the administrative power to foster the basic ideas involved and to translate them into general policy. We wish, too, to acknowledge the difficulties represented by resistance of a highly emotional nature that often stands in the way of administrators who wish to try out ideas of this

sort. We have a proper regard for the homely fact that, if all segments of the institution's staff are to cooperate fully, the theoretic materials must be shown to be practical in the most literal sense: the program must show not only that the staff's work will not be increased appreciably, but that it is also capable of establishing an improved record of results.

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Notes

THE TUBERCULIN REACTION IN PATIENTS ADMITTED TO A MILITARY TUBERCULOSIS SERVICE, 1958–1960

Increasing reliance upon the tuberculin test as a tool in tuberculosis case finding has renewed interest in the test itself, in the reactivity of patients, and in the significance of reactions to the test materials and dilutions employed in testing.

In former years it was usually found that nearly all tuberculous patients who were not gravely ill reacted to a skin test with the intermediate strength (5 TU) of purified protein derivative (PPD). For example, in 1942, Furcolow and associates[1] reported that 99.6 per cent of the patients in the Hamilton County Tuberculosis Hospital, Ohio, reacted to a test dose of 5 TU or less. Eleven years later, however, when Hewell and Suyemoto[2] repeated the same study in the same institution, they found that only 95 per cent of the tuberculous patients reacted to 5 TU or less. They did not consider chemotherapy to be responsible for the change, but thought that aging of the sanatorium population in the interval between studies might be a contributing factor. Lester and Atwell[3] reported an incidence of only 91.7 per cent of positive reactors to 5 TU or less among 624 patients tested at the Ohio Tuberculosis Hospital in 1958. Similar findings were reported in 1959 by Johnston and co-workers[4] at the Veterans Administration Hospital, Durham, North Carolina (93.9 per cent in 81 patients), and by Weir and Schless[5] at Fitzsimons Army Hospital (91.4 per cent in 498 patients). At the same time, these later observers found no evidence that tuberculin reactivity itself was vanishing, for nearly all of their tuberculous patients who failed to react to a test dose of 5 TU or less did react when tested with 250 TU. The change apparently was due to the degree of reactivity.

These reports, plus some sporadic observations of the present writers, raised the question of the adequacy of the 5-TU test dose for diagnostic purposes. Accordingly, the Tuberculosis Service of the U.S. Naval Hospital, St. Albans, New York, undertook a retrospective study of the tuberculin-test findings in patients admitted during a recent twenty-month period to ascertain: (*1*) how often it was necessary to resort to a test dose greater than 5 TU for diagnostic purposes; (*2*) the relationship, if any, between the need for a larger test dose and the extent of the tuberculosis present; (*3*) the effect, if any, of previous chemotherapy upon reactivity; and (*4*) whether or not patients who failed to react at the 5-TU level might exhibit recognizable characteristics which would identify them as a group.

Patients are referred to this service because of known or suspected tuberculosis. For diagnostic screening, they are routinely inoculated intradermally in the forearm with three commercially obtained materials: first-strength PPD (#1, 1 TU),[6] histoplasmin 1:100,[7] and coccidioidin 1:100.[8] The tests are given and interpreted in a central clinic within the department. Fresh solutions are mixed each day. Syringes are segregated to prevent cross-contamination with test materials. The tests are applied and interpreted within forty-eight hours by two hospital corpsmen trained and supervised by physicians.

First-strength PPD is used for initial testing to avoid the possibility of dangerous reactions in patients known or thought to have active tuberculosis.

Reactions are considered positive when indurations of 5 mm. or more result, measured in the greatest transverse diameter. Erythema alone is not considered to indicate a positive reaction. Patients with doubtful reactions (less than 5 mm.) are referred to a physician for interpretation of the test and re-examination at seventy-two hours if necessary. If test results remain questionable, they are recorded as negative.

If a patient does not react to first-strength PPD, intermediate-strength PPD (5 TU) is applied. If this is negative, second-strength PPD (#2, 250 TU) and/or Old Tuberculin[7] 1:100 are applied to separate forearms. If both of these tests are negative and clinical suspicion of tuberculosis still remains, they are repeated in three or four weeks before a final report is rendered.

For this study, the tuberculin reactions of 290 adult patients consecutively admitted to the U. S.

[1] Furcolow, M. L., *et al.*: Amer Rev Tuberc, 1942, *45*, 504.

[2] Hewell, B., and Suyemoto, D.: Amer Rev Tuberc, 1954, *69*, 733.

[3] Lester, C. F., and Atwell, R. J.: Amer Rev Tuberc, 1958, *78*, 399.

[4] Johnston, W. W., *et al.*: Trans 18th Conf on Chemother Tuberc, VA—Armed Forces, 1959, p. 155.

[5] Weir, J. A., and Schless, J. M.: Amer Rev Resp Dis, 1959, *80*, 569.

[6] Merck, Sharp and Dohme.

[7] Parke-Davis & Company.

[8] Cutter Laboratories.

Naval Hospital at St. Albans between July 1, 1958, and February 28, 1960, who subsequently were diagnosed to have active tuberculosis, were reviewed. The criteria for diagnosis of active tuberculosis included: appropriate historical, physical, and/or roentgenographic findings; the demonstration of tubercle bacilli on microscopy or culture; characteristic pathologic changes in resected specimens; recent tuberculin conversion; and pleurisy with effusion with positive tuberculin reactions in patients presenting no other apparent cause for illness. The data recorded for each patient were: strength of tuberculin at which a positive reaction developed, age, race, sex, diagnosis, bacteriologic findings, severity of illness, and previous treatment.

The 290 patients represented 242 cases of pulmonary tuberculosis; 43 cases of extrapulmonary tuberculosis, including pleurisy; and 5 cases of miliary-meningeal tuberculosis. The age, sex, and race distribution was that characteristic of a military hospital population: 248 patients (85.5 per cent) were less than forty years of age; 263 patients (90.7 per cent) were males; ethnically, 239 (82.5 per cent) were of European descent, 38 (13.1 per cent) were Negro, 12 (4.1 per cent) were Asian, and one man (0.3 per cent) was an American Indian. Apart from the tuberculosis, the majority of the patients were in good general health.

Subsequent study of the data showed that the age, sex, and race factors were similarly distributed whether the patients were grouped according to extent of disease or tuberculin reactivity.

In table 1, the 290 patients are grouped according to diagnosis and extent of disease, with the number and percentage of each group that reacted to 1 TU or 5 TU of PPD itemized. Of the total, 212 patients (73 per cent) reacted to 1 TU and an additional 51 patients (17.5 per cent) reacted when 5 TU were injected. Thus, 263 patients, or only 90.5 per cent of the total, reacted to PPD at a dosage of 5 TU or less.

The percentage of positive reactors to 1 or 5 TU in the separate diagnostic groups varied randomly, but the combined percentages remained near 90 per cent, with no correlation to extent of disease. Specifically, 89 per cent of the patients with minimal pulmonary tuberculosis, 94 per cent with moderately advanced lesions, 90 per cent with far advanced lesions, and 93 per cent with extrapulmonary lesions reacted to 5 TU or less. It was not necessary to exceed a dose of 1 TU to obtain a reaction in 4 of the 5 patients with miliary disease, although the fifth patient failed to respond to any test dose.

Expressed otherwise, about one-tenth of the patients with all forms of active tuberculosis, except miliary, did not react to 5 TU or less, and no correlation was evident between the extent of disease and decreased or increased reactivity to tuberculin.

Sixty-nine of the patients had received chemotherapy before admission to the hospital and, therefore, prior to the skin testing. Two were retreatment cases. The remaining 67 were patients who had received from two to sixteen weeks of initial treatment, usually with isoniazid and PAS, before the tuberculin reaction was determined.

To ascertain what effect, if any, such prior treatment had upon the reactivity of these patients to a test dose of 5 TU or less, the results were compared with those in the 221 previously untreated patients (table 2).

Twenty-four of the 69 previously treated patients had minimal disease, 16 had moderately advanced disease, 12 had far advanced, 15 extrapulmonary, and 2, miliary-meningeal tuberculosis. Eighteen of the 24 patients with minimal disease, 14 of the 16 with moderately advanced disease, and 10 of the 12 patients with far advanced tuberculosis reacted to 5 TU or less. All of the patients with extrapulmonary disease and one of the 2 patients with miliary-meningeal tuberculosis also reacted at this level.

In the contrasting group of previously untreated

TABLE 1

PATIENTS REACTING TO 1 OR 5 TU OF PPD

Diagnosis (Tuberculosis)	Total of Patients	Positive at 1 TU		Positive at 5 TU		Combined	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Pulmonary, minimal	125	91	73	20	16	111	89
Pulmonary, moderately advanced	77	62	80	10	14	72	94
Pulmonary, far advanced	40	24	60	12	30	36	90
Extrapulmonary	43	31	72	9	21	40	93
Miliary	5	4	80	0	0	4	80
	290	212	73	51	17.5	263	90.5

TABLE 2

PATIENTS REACTING TO 5 TU OR LESS: EFFECT OF TREATMENT BEFORE TESTING

Diagnosis (Tuberculosis)	Patients Treated before Testing			Patients Untreated before Testing		
	Total Tested	Number of Reactors	Per Cent of Reactors	Total Tested	Number of Reactors	Per Cent of Reactors
Pulmonary, minimal	24	18	75.0	101	93	92.1
Moderately advanced	16	14	87.5	61	58	95.1
Far advanced	12	10	83.3	28	26	92.9
Extrapulmonary	15	15	100.0	28	25	89.3
Miliary-meningeal	2	1	50.0	3	3	100.0
	69	58	84.0	221	205	92.8

patients, there were 101 instances of minimal tuberculosis, 61 of moderately advanced, 28 of far advanced, 28 of extrapulmonary, and 3 of miliary-meningeal tuberculosis. The number and percentage of patients in each of these categories who reacted to 5 TU or less were, respectively, 93 (92.1 per cent), 58 (95.1 per cent), 26 (92.9 per cent), 25 (89.3 per cent), and 3 (100 per cent).

It will be seen that, over-all, 84.0 per cent of the previously treated patients, in contrast to 92.8 per cent of the previously untreated patients, reacted at this level. In view of the small number of previously untreated patients, it is probably best to observe only that previous treatment may have reduced the reactivity slightly among the group as a whole.

The 27 patients with some form of active tuberculosis who failed to react to 1 or 5 TU were next tested with a dose of 250 TU in the form of PPD #2 and/or OT 1:100. The writers are well aware that the specificity of a 250-TU test dose is open to question but, as far as is known, the use of this dose for exclusion of disease in clinical diagnosis, as contrasted to case finding, has not been challenged.

The diagnosis of active tuberculosis was established bacteriologically in 22 of these patients, by the report of a "granuloma" in pleural biopsy material in one, and by roentgenographic improvement under treatment in the other 4 patients, all of whom were negative reactors to histoplasmin and coccidioidin.

A positive reaction at this dosage was achieved in 25 of the 27 patients (table 3). The 2 patients who still failed to react included a young man who was gravely ill with tuberculous meningitis when tested, and a 23-year-old asymptomatic man whose active minimal pulmonary disease was shown to be tuberculous by repeated recovery of *M. tuberculosis* in sputum cultures and by roentgenographic response to treatment. His failure to react to tuberculin was further investigated. The serum protein electrophoretic pattern was normal. A mumps serum complement-fixation titer was postive at a titer of 1:20, but no reaction occurred to mumps antigen administered intradermally. Some peculiarity of this patient's skin reactivity must be assumed.

When these 27 patients were compared with the others as to age, sex, and race distribution, they did not seem to differ materially. With one exception, all were less than forty years of age, all but 3 were whites, and 22 (81.5 per cent) were males. Thus, no appreciable difference could be detected between patients who reacted positively to 5 TU or less and those who did not.

The data in table 3 also show the results of simultaneously testing with PPD #2 and OT 1:100, and indicate that they are complementary test materials. Of the 25 patients with positive reactions, 22 reacted to PPD #2, but 3 reacted only to OT. All 3 patients represented bacteriologically proved cases of tuberculosis.

* * *

The results of this survey are similar to the findings reported previously[3-5] that about one-tenth of patients hospitalized with active tuberculosis fail to react to PPD tuberculin in a dosage of 5

TABLE 3

RESULTS IN 27 PATIENTS NEGATIVE AT 5 TU, TESTED AT 250 TU

Diagnosis (Tuberculosis)	Positive to PPD #2 Positive to 1:100 OT	Positive to PPD #2 Negative to OT*	Negative to PPD #2 Positive to OT	Negative to Both
Pulmonary, minimal	7	5	1	1
Pulmonary, moderately advanced	2	1	2	0
Pulmonary, far advanced	1	3	0	0
Extrapulmonary	1	2	0	0
Miliary	0	0	0	1
	11 (41%)	11 (41%)	3 (11%)	2 (7%)

* The OT test was not given to 6 patients, 4 with minimal, one with far advanced, and one with extrapulmonary disease.

TU or less. In the present series, the percentage of positive reactors was 90.5. This suggests that tuberculin sensitivity may be less in the patients encountered today than in former years. The prevalence of chemotherapy and the older average age of patients currently admitted to tuberculosis hospitals have been suggested as possible explanations of this change.

With respect to the role of chemotherapy, Steenken and Wolinsky[9] demonstrated a decrease in sensitivity in guinea pigs treated with isoniazid and repeatedly tested with tuberculin. However, similar studies among human patients by Criep and Levine,[10] and by Howell and Suyemoto[9] have failed to show this effect.

The present findings as to the effects of treatment upon reactivity are, as indicated above, inconclusive but suggest, if anything, that chemotherapy may decrease reactivity to tuberculin.

In respect to age factors, 85.5 per cent of the patients were less than forty years of age, and of the 27 patients who did not react to 5 TU or less, all but one were younger than forty. Of incidental note is the fact that the oldest patient in this series was a man of eighty-seven with advanced pulmonary disease who reacted strongly to a dose of 1 TU. Thus, old age, per se, could not be implicated in explaining the results.

Another factor of importance in skin testing that has only recently been emphasized is the instability of tuberculin solutions at high dilution due to adsorption of the tuberculin upon the glass of the syringe.[11-13] Adsorption is a complex physicochemical phenomenon depending on many things, and there are no quantitative data on the point in the present study. It is doubted, however, that adsorption was an important factor in the test results for two reasons: (*1*) test materials were diluted freshly each day, and the time for significant adsorption to occur in package vials was therefore minimized; and (*2*) the syringes themselves were kept segregated for use with tuberculin only; consequently, the surface available for adsorption was more likely to have become progressively reduced than increased.

By the use of 250-TU test doses, the percentage of reactors to tuberculin in this group of patients was increased to 99.3. It is not meant to imply that reaction at such dosage is specific for tuberculosis. Nonspecific reactions at this level have been well documented, as pointed out in the Edwards' recent review on tuberculin.[14] Nevertheless, by utilizing the present findings for their negative value, it could be said that, in differential diagnosis, if a patient does *not* react to PPD #2 or 1:100 OT, the probability of excluding tuberculosis from diagnostic consideration is increased from 90.5 per cent to 99.3 per cent.

In summary: Approximately one-tenth of a series of 290 patients with some form of active tuberculosis did not react to skin-test doses of 1 or 5 TU. Failure to react at the test-dose level of 5 TU or less was not correlated with extent of disease. There is some slight reason to believe that chemotherapy before testing may have decreased reactivity. A test dose of 250 TU, in the form of concomitant administration of second-strength PPD and OT 1:100, produced reactions in all but 2 of the patients who failed to react at the 5-TU level or less. This large test dose remains useful for purposes of exclusion in clinical diagnosis. The patients who reacted only to the maximal test dose had no group characteristics that distinguished them from the other tuberculous patients. The conclusion of other observers, that today's patients have a decreased degree of reactivity, is confirmed.

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September 26, 1960

[9] Steenken, W., and Wolinsky, E.: Amer Rev Tuberc, 1952, *65*, 365.

[10] Criep, L. H., and Levine, M. I.: Amer Rev Tuberc, 1953, *67*, 535.

[11] Parish, H. J., and O'Brien, R. A.: Brit Med J, 1935, *1*, 1018.

[12] Guld, J., *et al.*: Amer Rev Tuberc, 1955, *72*, 126.

[13] Waaler, H., *et al.*: Bull WHO, 1958, *19*, 783.

[14] Edwards, P., and Edwards, L.: Amer Rev Resp Dis, 1960, *81* (Supplement, p. 1).

RELIABILITY OF THE NIACIN TEST AS AN AID IN CLASSIFYING HUMAN AND BOVINE STRAINS OF TUBERCLE BACILLI IN EPIDEMIOLOGIC STUDIES[1]

Human infection caused by *Mycobacterium bovis* is still prevalent in many countries[2, 3] and in some of them it represents a problem of major importance because of its social and economic implications. In some countries, especially those with limited economic resources, the need for knowing the incidence of bovine tuberculous infections in their populations still exists[4]; in others, it is always important to conduct periodic surveys to ascertain if the hygienic measures under way are succeeding. Finally, in countries where bovine tuberculosis is no longer an important problem, it would seem worthy to re-evaluate previous observations periodically. These are some of the reasons why laboratory methods devised to simplify and efficiently improve differentiation of types of tubercle bacilli are welcomed.

The methods used until recently to differentiate *Mycobacterium tuberculosis* and *M. bovis* were based mainly on the cultural characteristics of strains grown on several culture media, usually on Löwenstein-Jensen medium, and the virulence of both species for guinea pigs and rabbits. Recently, Konno[5] proposed a chemical method to distinguish human strains of tubercle bacilli from all other mycobacteria. The method is based on the fact that human tubercle bacilli, under appropriate conditions, produce significantly greater amounts of niacin than other mycobacteria.

The purpose of the present paper is to report results obtained in evaluating the niacin test as an aid to differentiate strains of human and bovine tubercle bacilli in an epidemiologic survey, in comparison with the more conventional procedures mentioned above. It was also desired to determine the incidence of bovine bacilli in a significant number of strains isolated from Mexican tuberculous patients.

The present typing included 1,091 strains of tubercle bacilli isolated from 4,000 specimens. With the exception of cerebrospinal fluids, all specimens were homogenized with 4 per cent sodium hydroxide; the sediment after centrifugation was neutralized with 5 per cent hydrochloric acid, and 0.2 ml. was inoculated into each of two tubes of Löwenstein-Jensen medium which contained 0.6 per cent glycerol. The Subcommittee of Laboratory Methods of the International Union Against Tuberculosis states that a glycerol concentration up to 0.75 per cent is not inhibitory for bovine tubercle bacilli in egg media and thus it can be used for their primary isolation from human sources.[6] Cerebrospinal fluids were merely centrifuged and cultured as were the other specimens.

Three general procedures were used for properly typing the strains: cultural characteristics such as colonial morphology, rate of growth, and pigment production; niacin content; and virulence for guinea pigs and rabbits. Difficulties in distinguishing between human and bovine bacilli have previously been emphasized.[7] Nevertheless, differentiation is relatively easy to achieve because of the differences in their niacin content and pathogenic characteristics. Differentiation of bovine from avian or nonphotochromogenic strains is more difficult; some discussion of how to differentiate some of these groups is presented below.

Selection of strains: Only 6 strains of mammalian tubercle bacilli were subjected to differentiation. Strains which grew at primary isolation after ten days or less of incubation, usually giving mucous colonies either pigmented or nonpigmented, were considered as unclassified mycobacteria and, therefore, are not included in the present survey.

Scotochromogenic strains were easily distinguished by the orange-pigmented colonies they produced. Photochromogenic strains were not found at all. Rapidly growing strains either pigmented (*Mycobacterium smegmatis, Mycobacterium phlei,* et cetera) or nonpigmented (*Mycobacterium fortuitum*-like) were distinguished from all other strains by their rate of appearance of growth. Finally, bovine strains were differentiated from the avian nonphotochromogenic group of strains by assessing their virulence for guinea pigs and rabbits. Only bovine strains produced gross tuberculosis in both of these animals. Caution was taken with the mammalian strains resistant to isoniazid which displayed only limited virulence for the guinea pig,[7] a phenomenon which often gives place to confusion in the differentiation; indeed, this was found to be the case with a number of strains. Most of the findings made on unclassified mycobacteria during this work have already been reported.[8]

[1] Supported, in part, by funds from the National Committee of Fight Against Tuberculosis, México, D.F.

[2] Von Urech, E.: Tuberkulosearzt, 1957, *11*, 733.

[3] Francis, J.: Tuberculosis in Animals and Man, Cassell and Co., London, 1958.

[4] Bauza, J. A.: Arch Pediat Urug, 1958, *129*, 815.

[5] Konno, K.: Science, 1956, *124*, 985.

[6] Jensen, K. A.: Bull Un Int Tuberc, 1954, *24*, 78.

[7] Middlebrook, G., and Cohn, M. L.: Science, 1953, *118*, 297.

[8] Bojalil, L. F.: Amer Rev Resp Dis, 1961, *83*, 597.

Niacin tests: Qualitative tests for niacin content were carried out in all strains studied. Two different methods were used: (*1*) following isolation in Löwenstein-Jensen medium, the strains were subcultured on a modified Proskauer and Beck medium[9]; after one month of incubation at 37°C., the whole culture was added with 0.5 ml. of 4 per cent (v/v) aniline in 95 per cent ethanol and 0.5 ml. of a 10 per cent (w/v) aqueous solution of cyanogen bromide. Positive results characteristic of human strains were evidenced by development of an intense yellow color in the medium; (*2*) a spot test technique was simultaneously performed with a tetracycline developed in this laboratory.[10] These tests were carried out using recent isolates, provided the growth that developed was abundant. When the growth of the primary cultures was not enough to provide extracts for the spot test, the strains were subcultured on Löwenstein-Jensen medium and then extracted.

Virulence for guinea pigs and rabbits: Not all isolated strains were inoculated into animals. The strains inoculated were especially those isolated from extrapulmonary lesions and those which gave negative or dubious niacin tests; a considerable number of niacin-positive strains were also inoculated as controls. The guinea pigs used weighed 350 to 450 gm. while the rabbits weighed 3 to 3.5 kg. One guinea pig and one rabbit were inoculated per strain. All animals were kept in individual cages and, prior to inoculation, all were negative to the subcutaneous injection of 0.2 ml. of a 1:5 dilution of Old Tuberculin. Twenty-one-day-old cultures grown in Löwenstein-Jensen medium were ground in mortars using saline as diluent. The bacterial mass was determined in Hopkins tubes; 0.02 mg. wet weight of bacilli was injected subcutaneously in the anterior aspect of the right thigh of guinea pigs or through the marginal vein of the right ear of rabbits. If the animals did not die three months after inoculation, they were sacrificed to determine the presence of lesions.

Those strains that gave positive niacin reactions and produced generalized tuberculosis in the guinea pig but not in the rabbit were considered to be human tubercle bacilli. Determinations of susceptibility to isoniazid were performed when the strains did not cause gross tuberculosis in the guinea pig; in such cases, the results obtained with the niacin tests were taken as definite criteria.

Those strains that produced generalized tuberculosis in both guinea pigs and rabbits and gave also negative niacin reactions were considered to be bovine strains.

Nonvirulent strains for guinea pigs and rabbits which gave negative niacin reactions were included in the avian nonphotochromogenic group, and, therefore, are not considered in the results.

[9] Youmans, G. P., and Karlson, A. G.: Amer Rev Tubere, 1947, *55*, 529.

[10] Gutiérrez-Vázquez, J. M.: Rev Lat Amer Microbiol, 1958, *1*, 287.

TABLE 1

Source of Tubercle Bacilli Strains Studied

Source	Pulmonary	Extra-pulmonary
Adults, General Hospital, Mexico City	694	45
Adults, Acapulco, Gro, Mexico	203	
Children, Children's Hospital, Mexico City	90	59
Total	987	104

In table 1 it may be seen that 987 of a total of 1,091 strains of tubercle bacilli studied were isolated from patients with pulmonary tuberculosis, while 104 were isolated from patients with extrapulmonary disease. The source of the extrapulmonary strains is given in table 2.

Twenty of 1,091 strains failed to give positive niacin reactions in primary cultures. Of these 20 niacin-negative or doubtful strains, 10 were positive after one subculture into fresh medium, while one strain was positive only after a second subculture in Löwenstein-Jensen medium. Of the remaining 9 negative or doubtful niacin-negative strains, 4 gave positive reactions only after being recovered by culture from guinea pig organs, while the other 5 strains were finally classified as *M. bovis*. The 5 strains classified as *M. bovis* always gave negative niacin reactions, except one which gave a doubtful reaction (table 3). The final classification of these strains was supported by their high pathogenicity in rabbits.

A total of 254 strains were inoculated into laboratory animals (table 4). All niacin-positive strains led to generalized tuberculosis in guinea pigs and were nonpathogenic for rabbits, except for three strains which were of low virulence for guinea pigs but were resistant to 10 γ or more of isoniazid per ml. of medium; therefore, all of them were classified as human strains.

TABLE 2

104 Extrapulmonary Strains of Tubercle Bacilli Studied

Site of Lesion	Children up to 10 Years	Children Older than 16 Years
Abdominal organs	—	19
Meninges	37	5
Bones and joints	8	5
Skin	9	6
Cervical lymph nodes	5	10
Total	59	45

TABLE 3

RESULTS OF THE NIACIN TESTS CARRIED OUT ON 1,091 STRAINS OF TUBERCLE BACILLI

	First Test*	Second Test†	Third Test‡	Fourth Test§	Final Status
Number of tests done	1,091	20	10	9	
Niacin positive	1,071	10	1	4	1,086
Niacin doubtful	2	3	5	1	1‖
Niacin negative	18	7	4	4	4‖

* In primary cultures. When the growth obtained in primary cultures was not sufficient to carry out niacin tests, the strains were subcultures; results obtained with these subcultures are referred to as primary cultures.

† Subcultures of strains doubtful or negative in first test.

‡ Subcultures of strains doubtful or negative in second test.

§ Doubtful or negative strains after the third test which were recovered from the organs of guinea pigs.

‖ These strains were finally classified as bovine.

Only one strain exhibited a certain degree of pathogenicity in rabbits with the inocula injected; this strain was inoculated into as many as 5 rabbits with similar results. It was finally classified as *M. tuberculosis* on the basis of the positive niacin test it consistently gave.

Four strains which always were weakly positive for niacin and were pathogenic for guinea pigs but not for rabbits were also classified as corresponding to the human strain. These strains gave positive niacin tests only after being recovered by culture from guinea pig organs, as previously mentioned.

Four of the 5 bovine strains found were isolated from patients with pulmonary tuberculosis, while the other one strain was isolated from an autopsied patient who had died of intestinal tuberculosis. No bovine strain was isolated from children. The overall incidence of bovine tuberculosis found is 0.46 per cent (table 5). These results suggest a low incidence of bovine tuberculosis in the human population in Mexico, much lower than that previously reported.[11] The present findings may be due to the extent to which pasteurized and dehydrated milk are consumed nowadays, as well as to the widespread habit of boiling milk before ingestion.

* * *

Results obtained with the use of the niacin test clearly show the usefulness of this method as an important aid for classifying tubercle bacilli in epidemiologic surveys. The niacin test has the advantages of being reproducible, easy and rapid to make, and more economic than any other method.

[11] OLARTE, J., AND VERGARA, J.: Bol Med Hosp Infant (Mex), 1953, *10*, 673.

TABLE 4

PATHOGENICITY OF 254 STRAINS OF TUBERCLE BACILLI FOR GUINEA PIGS AND RABBITS

Niacin and Virulence Characteristics	Number of Strains		Final Classification
	Pulmonary	Extrapulmonary	
Niacin positive, highly virulent for guinea pigs but not for rabbits	141*	102	Human
Niacin positive, highly virulent for guinea pigs; slightly virulent for rabbits	1	1	Human
Niacin weakly positive; highly virulent for guinea pigs but not for rabbits	4†		Human
Niacin weakly positive; highly virulent for both guinea pigs and rabbits	1		Bovine
Niacin negative, highly virulent for both guinea pigs and rabbits	3	1	Bovine
Total inoculated	150	104	

* Three of these strains did show low virulence for guinea pigs. It was further demonstrated that they were resistant to at least 10γ of isoniazid per ml. of medium.

† As shown in table 3, these strains gave positive niacin reactions after recovery from guinea pig organs.

TABLE 5

FREQUENCY OF TYPES OF TUBERCLE BACILLI STRAINS

	Number of Strains	Human	Bovine	
			Number	Per Cent
Pulmonary	987	983	4	0.40
Extrapulmonary	104	103	1	0.96
Total	1,091	1,086	5	0.46

Pathogenicity for guinea pigs and rabbits could be confined only to strains that give negative or doubtful niacin reactions. Differentiation merely by colonial morphology does not promote confidence, since different groups of mycobacteria, *i.e.*, *M. bovis* and the avian nonphotochromogenic group, have similar morphologic characteristics. Moreover, some strains of mammalian tubercle bacilli would eventually appear quite atypical, thus allowing either of two strains to be mistaken for each other. For instance, some human strains when grown on solid medium containing distilled water may develop smooth colonies practically indistinguishable from those of other mycobacteria, and it is only after one or more subcultures that they develop colonies with their characteristic morphology.

The pathogenicity for laboratory animals is a very reliable method for classifying mammalian strains of tubercle bacilli, although it is expensive and time consuming, thus being impractical for epidemiologic surveys. Nevertheless, it is useful as a complementary method.

One of the remaining problems is the differentiation of bovine bacilli from the avian nonphotochromogenic group. Having similar colonial characteristics, it was possible to distinguish them only by pathogenicity tests. Differentiation by means of their nicotinamidase activity[12, 13] will probably be of great help in the future.

In summary: A survey was made on 1,091 strains of mammalian tubercle bacilli to differentiate between human and bovine strains. Classification was based on colonial morphology, pathogenicity for guinea pigs and rabbits, and niacin tests. It was found that the niacin test is of great help for this type of study. Pathogenicity for laboratory animals has the drawback of being expensive, time consuming, and laborious, and should be limited only to those strains that fail to give positive niacin reactions on primary cultures. The over-all incidence of *Mycobacterium bovis* in 1,091 strains, including 987 pulmonary and 104 extrapulmonary cases, was only 0.46 per cent.

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December 29, 1960

[12] Bönicke, R., and Lisboa, B. P.: Tuberkulosearzt, 1959, *13*, 377.

[13] Konno, K., *et al.*: *a.* Nature, 1959, *184*, 1743. *b.* Amer Rev Resp Dis, 1960, *81*, 550.

SPUTUM INDUCTION WITH HEATED AEROSOL INHALATIONS FOR THE DIAGNOSIS OF TUBERCULOSIS

When patients under examination for pulmonary tuberculosis produce little or no sputum for bacteriologic study, gastric washings are usually obtained. The inadequacies of gastric washings and the danger of contagion associated with tracheobronchial lavage or laryngeal swab techniques led to trials of aerosol inhalations to increase sputum production.[1-3] In those studies, sputum obtained following inhalation of an aerosol of normal saline or distilled water was positive for tubercle bacilli more often than were gastric or tracheobronchial lavage specimens. Unfortunately, in none of those reports was it stated whether the patients were able to produce sputum prior to aerosol inhalations. Thus, the contribution of nebulization to the results achieved is not clear.

The following study of 87 hospitalized male patients, who were raising little or no sputum, compares gastric washings with sputum induced by inhaling a heated, hypertonic aerosol for the diagnosis of pulmonary tuberculosis. Some of the patients were suspected of having tuberculosis, and others were already being treated for pulmonary tuberculosis.

Except for the modifications described below, the equipment and techniques used were those described by Barach and associates.[4,5] The solution to be nebulized, 10 per cent sodium chloride and 10 per cent glycerin in water, was poured into the inner cup and placed in the outer pot, which was approximately one-third filled with water (figure 1). The top was then fitted into the outer pot, as shown. The glass mouthpiece supplied by the manufacturer was discarded as being too fragile; it was replaced with one made by joining together with silver solder two plumber's ¾-inch copper street elbows, and then chrome-plating them. This mouthpiece had an internal pathway about 14 cm. in length, with two 90°-angle turns. The nebulizer was driven by a diaphragm type of air compressor. The extra air inlet was closed, and the patient was instructed to inhale the warm aerosol while holding his mouth as close to the mouthpiece opening as comfort allowed (figure 2). After the initial heating surge, the aerosol temperature at the mouthpiece varied around 50°C. An expiratory-inspiratory-pause breathing rhythm prevented hyperventilation and enhanced aerosol retention in the lungs.[6] The ward nurses set up the apparatus and instructed the patient in its use, but they did not continuously supervise the nebulization. Any sputum produced by voluntary coughing during forty-five minutes of nebulization and the following hour was collected and sent to the laboratory for a Ziehl-Neelsen stain of a direct smear, a smear of concentrate (Darzins' SP method[7]), and culture on one tube of Löwenstein-Jensen medium. Gastric washings were obtained from the same patient before breakfast the same morning, or within seven days, and were subjected to identical concentration and culture techniques. Cultures were incubated eight weeks before being reported negative. Patients yielding unclassified mycobacteria were excluded from the study. The top and inner cup of the nebulizer were autoclaved prior to use. The outer pot could not be immersed in water or autoclaved. It was washed and filled with 70 per cent ethyl alcohol for thirty minutes to kill tubercle bacilli.[8]

It may be seen in table 1 that tubercle bacilli were identified from sputum obtained by nebulization almost twice as often as from paired gastric washings ($P < 0.01$). The details of these findings are shown in table 2. Due to the type of patients selected for this study, viz., those producing little or no sputum, more than 80 per cent of the specimens were negative for tubercle bacilli. It is noteworthy that 22 sputum specimens obtained by nebulization were positive for *M. tuberculosis* when the paired gastric washings were negative. The reverse combination of negative nebulized sputum and positive gastric washings occurred only three times. Thus, if gastric lavage had been omitted in these 232 examinations, culturable tubercle bacilli would have been missed on only three occasions (two cultures containing one colony and one culture containing three colonies). Paired nebulized sputum and gastric lavage specimens were both positive for tubercle bacilli in 17 instances, but the finding of acid-fast bacilli on

[1] Garcia, D. E.: Bol Asoc Med P Rico, 1952, *44*, 198.

[2] Payne, H. M., *et al.*: Trans 15th Conf on Chemother Tuberc, VA, Army & Navy, 1956, p. 227.

[3] Warembourg, H.: Rev Tubere (Par), 1958, *22*, 719.

[4] Barach, A. L., *et al.*: AMA Arch Intern Med, 1960, *106*, 230.

[5] The super-heated nebulizer and the air compressor motor were obtained from Inhalational Equipment Co., Inc., 1686 Second Avenue, New York 28, N. Y.

[6] Miller, W. F.: New Engl J Med, 1954, *251*, 589.

[7] Darzins, E.: The Bacteriology of Tuberculosis, University of Minnesota Press, Minneapolis, 1958.

[8] Smith, C. R.: Public Health Rep, 1947, *62*, 1285.

FIG. 1 (Left). Components of heated nebulizer.
FIG. 2 (Right). Air compressor and heated nebulizer in use.

microscopy in 14 of these nebulized sputum specimens was available much earlier than with the gastric culture. Unsatisfactory cultures (dried, acid, contaminated, et cetera) occurred in 18 per cent of the nebulized sputum specimens and in 17 per cent of the gastric lavage specimens.

No serious side effects from nebulization were noted. Occasional patients reported slight upper respiratory tract irritation or nausea that disappeared shortly after completion of nebulization. Two patients noted aggravation of previously present "sinus trouble," but subsequent nebulization of one of these patients with normal saline instead of hypertonic solutions was accomplished without symptoms.

Unfortunately, it was not possible to obtain an exact count of those patients who inhaled the nebulized solution but were still unable to produce sputum. Other investigators have reported that warm, hypertonic aerosol inhalations induced sputum in 73 to 86 per cent of patients who were previously raising little or no sputum.[9-11]

TABLE 1

IDENTIFICATION OF TUBERCLE BACILLI FROM PAIRED GASTRIC WASHINGS AND SPUTUM OBTAINED BY NEBULIZATION

Procedure	Positive for Tubercle Bacilli	Negative or Unsatisfactory Results	Total
Nebulized sputum*	39	193	232
Gastric washings†	20	212	232

$X^2 = 7.0 \quad (P < 0.01)$

* Includes both microscopy and culture.
† Includes culture only.

TABLE 2

DETAILS OF MICROSCOPY AND CULTURE COMBINATIONS OF PAIRED GASTRIC WASHINGS AND SPUTUM OBTAINED BY NEBULIZATION

A. Gastric washings negative for tubercle bacilli*	22
Nebulized sputum positive for tubercle bacilli as follows:	
Microscopy + culture + = 4	
Microscopy + culture − = 5	
Microscopy − culture + = 13	
B. Gastric washings positive and nebulized sputum negative for tubercle bacilli:	3
C. Gastric washings positive for tubercle bacilli	17
Nebulized sputum positive for tubercle bacilli as follows:	
Microscopy + culture + = 13	
Microscopy + culture − = 1	
Microscopy − culture + = 3	
D. Gastric washings negative and nebulized sputum negative for tubercle bacilli:	190
Total pairs compared	232

* "Negative" includes both unsatisfactory cultures and cultures without growth at eight weeks.

[9] BICKERMAN, H. A., *et al.*: Dis Chest, 1958, *33*, 347.
[10] BERKSON, D. M., AND SNIDER, G. L.: JAMA, 1960, *173*, 135.
[11] UMIKER, W. O., *et al.*: New Engl J Med, 1960, *262*, 555.

* * *

A number of more or less arbitrary decisions were necessary in setting up the neublization procedure. A brief review of these issues may be helpful.

An intelligent choice of nebulizer requires a knowledge of the droplet-size distribution of the aerosols produced, because that determines the penetration and retention of the aerosol in the respiratory tract.[12] Such measurements have not been reported for the nebulizer used in this study. Therefore, it is not known how much of this nebulizer's relatively high output reaches the lower respiratory tract and aids sputum production.

Although the nebulizer has been used with its air inlet closed, which gives a somewhat higher aerosol temperature, Barach and co-workers[4] have recently pointed out that the nebulizer output is greater with the inlet open. If the patient is instructed to close his lips on the mouthpiece and breathe through the nebulizer, the air inlet must be open.

Because concentrated solutions of propylene glycol kill tubercle bacilli,[13] glycerin was used as the hygroscopic agent. On the other hand, 10 per cent glycerin has been reported to be "pneumo-constricting," whereas 10 per cent propylene glycol has the opposite effect. Ten per cent sodium chloride has no such effect.[13] Although bronchodilator drugs were not included in the present study procedure, their use in selected cases might improve distribution of the aerosol and aid in effective coughing.

[12] Dautrebande, L.: Physiol Rev, 1952, *32*, 214.
[13] Potter, T. S.: Science, 1944, *99*, 406.

The total of one hour and forty-five minutes used in this study for sputum induction and collection is probably short enough to be useful for outpatients, from whom useful gastric washings are difficult to obtain. In hospitalized patients who fail to produce sputum after forty-five minutes of nebulization, repeated aerosol inhalations several times a day might be more successful. It has not been shown that aerosol inhalations will affect the diagnosis of pulmonary tuberculosis if sputum is already being produced spontaneously.

Although the nebulization procedure as used provided a better specimen than gastric lavage for identification of tubercle bacilli, it is not certain which aspects of the procedure contributed to its success. Further study is necessary to indicate what features are critical, but the importance of using a heated nebulizer with a high output of aerosol of the appropriate droplet-size distribution seems to be well established.

In summary: In patients suspected of, or undergoing treatment for, pulmonary tuberculosis who produced little or no sputum, tubercle bacilli were identified more often from sputum induced by inhaling a heated aerosol of 10 per cent glycerin and 10 per cent sodium chloride in water than from gastric washings.

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PRELIMINARY STUDIES IN THE USE OF SUPERHEATED SALINE NEBULIZATION IN THE BACTERIOLOGIC DIAGNOSIS OF PULMONARY TUBERCULOSIS

A problem in the diagnosis of tuberculosis has been the difficulty of obtaining adequate sputum specimens from some patients. Bickerman and associates[1] showed that a solution of 10 per cent saline and 20 per cent propylene glycol utilized as a superheated aerosol can, in a high percentage of cases, produce suitable sputum specimens. They obtained an adequate mucoid sputum specimen and adapted this principle to the cytologic diagnosis of cancer of the lung. The time of nebulization ranged from 11.7 to 15.0 minutes. Umikar and co-workers[2] recently confirmed the work of Bickerman and his associates.

On the basis of these reports, attempts were made to produce artificial sputum in tuberculous patients who had either no cough or an ineffectual cough. A total of 84 patients was studied; 66 patients were classified as having inactive tuberculosis, 6 patients had recently had sputum negative on microscopy, and 6 patients were being observed for possible tuberculous activity. In addition, 6 patients with possible pulmonary neoplasm had cytologic specimens produced by this method.

Essentially, the method described by Bickerman and co-workers was utilized. Certain modifications were adopted for the initial examinations with the superheated steam nebulization method. In order to avoid undue irritation, an arbitrary time limit of ten minutes was adopted for use of the nebulization, unless patients had productive cough prior to this time. Initially, if a patient failed to have productive cough during this time the test was considered a failure (3 patients). However, in subsequent tests patients who did not have a spontaneously induced cough within ten minutes were urged to cough voluntarily. In all but one case the sputum obtained was sufficient for examination. To avoid any possible chance of contamination, a disposable cardboard mouthpiece was used for each patient. The patient was instructed to hold his mouth one inch from the mouthpiece and to inhale the aerosol during each normal inspiration, the end point being productive cough. Only one trial (with rare exceptions) was utilized per patient during the initial experiment.

It had been this laboratory's policy to obtain tracheal and, usually, gastric specimens in patients without productive cough. It was of interest to compare the results of sputum obtained by nebulization with tracheal (and occasionally gastric) lavage specimens obtained during the same day period. From the type of patients selected it was evident that the majority of bacteriologic specimens would be negative for tubercle bacilli. It was also found advisable to separate patients according to their smoking habits and past coughing history.

In 84 patients an attempt was made to produce sputum artificially. Seventy-eight patients had inactive or active tuberculosis, predominantly the former. In 74 patients of this group, adequate specimens were obtained which were compared with tracheal lavage specimens (often pooled with gastric lavages) obtained earlier in the day. The sputum from 70 patients was negative for tubercle bacilli by both methods. In 3 patients whose specimens were previously intermittently positive for tubercle bacilli but who could no longer produce adequate sputum, positive smears and cultures were obtained by both methods. The Gaffky count and culture growth correlated well when both methods were compared. One patient with a questionably positive (single colony of tubercle bacilli) tracheal lavage yielded no tubercle bacilli with the nebulization technique. However, this patient's disease has remained clinically and roentgenographically inactive.

In practically all cases the sputum produced by nebulization was superior to tracheal lavage as it appeared mucoid-to-purulent and was considered to represent true bronchial secretion. The sputum obtained varied from 2 to 8 ml., and was ample for diagnostic purposes. A cough was successfully induced within ten minutes in 71 of 84 patients (85.4 per cent). The average time for this group was three minutes, with a range of thirty seconds to ten minutes. Ten of 13 patients failed to cough within the ten-minute period with the nebulization technique and were instructed to cough voluntarily. Thereupon, all but one produced adequate sputum for examination.

The failure of some patients to develop a productive cough following nebulization appeared to be generally related to previous smoking habits and coughing history. Seven of 13 patients (62 per cent) who did not cough after nebulization were nonsmokers. On the other hand, 89 per cent of smokers coughed readily with nebulizer stimulation.

Eleven of 13 patients who failed to cough had

[1] Bickerman, H. A., *et al.*: Dis Chest, 1958, *33*, 347.

[2] Umikar, W. O., *et al.*: New Engl J Med, 1960, *262*, 565.

no previous history of cough. Of 71 patients who had induced cough, 20 had no previous history of cough; 37 had mild, poor, or dry cough; while one had a productive cough on occasion.

There were only two minor side effects. One patient developed a mild wheeze following nebulization; he was a mild asthmatic. The second patient had an episode of vomiting following an induced cough.

The results indicate the feasibility of using sputum obtained by means of the superheated saline (10 per cent) with propylene glycol (20 per cent) nebulization in the bacteriologic diagnosis of pulmonary tuberculosis. The majority of the patients elected had inactive tuberculosis, and it was evident that their sputum would be free from tubercle bacilli. However, the excellent correlation, both negative and positive, between tracheal lavage specimens (pooled frequently with gastric lavages) and nebulizer-induced sputum demonstrated that the aerosol method has great utility. This is particularly so in tuberculous or suspected tuberculous patients who do not have productive cough. At the present time, the majority of patients in this hospital who do not have adequate sputum are utilizing this method. The writers are in the process of further correlating the bacteriologic results of simultaneous tracheal lavage and machine-induced sputum specimens in patients who have just become noninfectious and in those patients whose disease appears to be active on roentgenography but whose sputum contains no tubercle bacilli.

Practical advantages to the nebulization-produced sputum have been found when compared to the traditional method, namely: (*1*) nebulization may be self-administered after instruction, in contrast to the gastric and tracheal lavage methods which require nursing or medical supervision and administration; (*2*) the nebulizer method is less traumatic for the patient; (*3*) it may be used postprandially; (*4*) adequate sputum can usually be obtained within an average time of three minutes; (*5*) the method can be used in certain psychotic patients, possibly because of the repetitive nature of the procedure.

It is significant that 13 of 84 patients failed to produce sputum within an arbitrarily set time limit of ten minutes. It is probable that, if a longer period of time were allowed and if re-runs were routinely tried, a higher percentage of induced cough may have resulted. In one patient who was resistant to cough production, nebulization was tried three times and was ineffective. The decreased time necessary to induce cough in this series, as compared to the studies of Bickerman and associates, is ascribed to the predominance of patients with recent and present bronchial irritation or infection in the present series.

The correlation between a patient's ability to induce cough within ten minutes and his previous smoking and coughing history is of interest. Seven of 13 patients who failed to cough (62 per cent) were nonsmokers, 63 of 71 who were successfully induced to cough (89 per cent) were smokers, and 11 of 13 who could not be made to cough (85 per cent) had no histories of previous cough. It is possible that previous bronchial infections or irritants such as smoking may afford the bronchial tree a different threshold to cough stimulation. In support of this, the results of Bickerman and his co-workers are important. They found positive results in 86 per cent of patients without evidence of pulmonary disease, in 90 per cent of patients with pulmonary disease, and in 100 per cent of patients with carcinoma of the lung. Tiffeneau[5] states that acetylcholine will produce a rapid and prolonged cough in patients with respiratory diseases, and he has devised a test based on this premise. Based on these findings, it is possible that a test could be developed which utilizes superheated steam in a quantitative manner so as to determine the degree of bronchial irritation or even the extent of past smoking habits in a given individual.

In summary: The production of sputum by means of the superheated saline nebulizer is useful in the bacteriologic diagnosis of tuberculosis. This method is particularly valuable in patients who do not have a productive cough. The bacteriologic findings in sputum obtained by nebulization correlated well with those obtained by tracheal and gastric lavage. The average time necessary to produce a cough by the nebulization method in 85.4 per cent of the patients was three minutes.

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[5] TIFFENEAU, R.: Dis Chest, 1957, *31*, 404.

A SIMPLE METHOD FOR THE CULTIVATION OF MYCOBACTERIUM TUBERCULOSIS

Today the eradication of tuberculosis, or at least a reduction of its incidence to a level at which the disease ceases to be a public health problem, is an exciting possibility. The skillful use of formal therapy, vaccination prophylaxis, and prophylactic chemotherapy alone will do much to bring this about.

In many metropolitan communities with their highly developed health services, these objectives are close. In the underdeveloped countries they are far from achievement. Here among other things, limitations are imposed by the lack of trained personnel and equipment, and the need is for simplified but effective techniques. In no field is this need more urgent than in bacteriology. It is unnecessary to stress the crucial importance, in tuberculosis control, of bacteriology in diagnosis and management of patients.

Examination by microscopy of relevant material is widely used, but it has its limitations, and our aim should be to culture the bacillus. It is commonly the case in the underdeveloped countries that classical methods of culture are not practicable.

This paper describes a simple method of culture of *Mycobacterium tuberculosis* which needs no elaborate equipment and can be undertaken by a comparatively untrained staff safely and satisfactorily. The method has been used with success in the Territory of Papua and New Guinea for the past nine months.

Medium: The medium described in this paper is a modified Löwenstein Jensen preparation which is cheap, keeps well in tropical conditions, can be transported without damage, and gives a good color contrast with growing colonies. Solid media are to be preferred to liquid media, which commonly need re-examination on solid plates, tend to be more easily liable to contamination, and expose untrained staff to more dangers than is the case with solid media.

Materials and manufacture: The materials needed are as follows:

Two dozen medium-sized fresh eggs		
Potassium dihydrogen phosphate	2.40	gm.
Magnesium sulfate ($MgSO_4 7H_2O$)	0.24	gm.
Magnesium citrate	0.60	gm.
l-asparagine	3.60	gm.
Glycerin	12.00	ml.
Distilled water	600.00	ml.

The eggs should be scrubbed with soap and water, cleaned with methylated spirit, and allowed to dry. The other ingredients are dissolved in distilled water in a sterile half-gallon glass jar, which is then placed in a water bath and steamed for one hour.

The eggs are broken and placed in a second half-gallon jar into which a half pound of coarse glass beads has previously been placed. The whole is vigorously shaken until the eggs are homogenized. The egg solution is then filtered through sterile gauze into the cooled salt solution, and 20.00 ml. of 2 per cent malachite green solution are added. The mixture is mixed thoroughly. (Masks are worn throughout the process.) A rubber cork equipped with a simple dispensing apparatus (sterilized) is fitted into the jar, which is then mounted on a metal laboratory stand and fastened securely (figure 1).

The medium is dispensed into McCartney Universal containers (30 ml. capacity), 5.00 ml. being placed in each. The containers are sterilized prior to filling by autoclaving containers and screw tops separately.

Preparation of medium for drug-resistance tests and controls: For this purpose 16-ml. screw-capped medium bottles are used.

Solutions of streptomycin, para-aminosalicylic acid (PAS), and isoniazid are prepared. All are made in 0.1 per cent solutions.

Two flasks, one containing 0.25 ml. and one containing 2.50 ml. are prepared from each of the parent solutions, and to these 50.00 ml. of medium are added. The preparations, now containing 5 γ and 50 γ per ml., respectively, of the parent substances are dispensed into marked sterile half-ounce containers, each of which receives 2.00 ml.

Inspissation: After filling, the containers are placed on trays in a sloping position and inspissated for forty minutes at temperatures between 85° and 95°C. For this the steam autoclave is used. If an autoclave is not available, a boiling water sterilizer can be used. The trays are placed two inches and more above the boiling water. Temperature control (by thermometer) can be achieved by raising or lowering the lid of the sterilizer. Both methods have been used. No contamination of the medium has been noted before inoculation.

Medium prepared in this way will keep well at ordinary tropical conditions for three months. Growth usually occurs on medium six months old, but the results are variable, and it is recommended that medium more than three months old not be used. Transport of the medium by air is not a problem provided the rubber-sealed caps are screwed securely.

Inoculation: Inoculation is carried out in a closed room if possible, without draughts, and face masks are worn.

Two methods of sputum culture can be used.

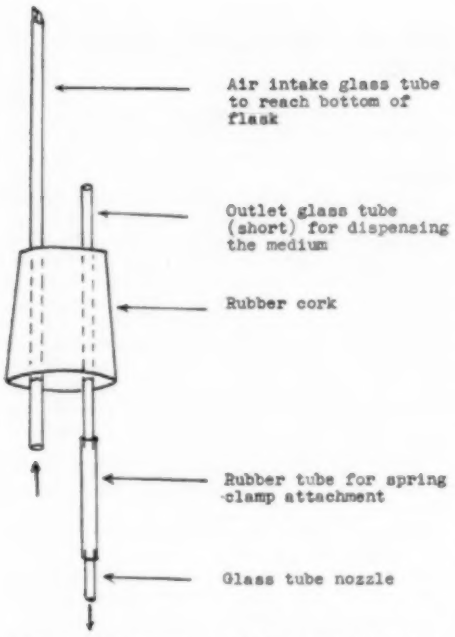
Air intake glass tube to reach bottom of flask
Outlet glass tube (short) for dispensing the medium
Rubber cork
Rubber tube for spring clamp attachment
Glass tube nozzle

FIG. 1. Attachment to medium-containing flask for dispensing. The medium is measured out, pressing the spring clamp, by visual control only.

First method: A small selected specimen of sputum is taken up on a sterile swab and immersed for fifteen minutes in 5 per cent oxalic acid. It is then removed from the solution and immediately rubbed onto the surface of the medium. Two slopes are inoculated for each specimen.

Second method: Two to five milliliters of sputum are collected directly into a one-ounce McCartney container. Twice the volume of 5 per cent oxalic acid is added, and the whole is shaken vigorously. The material is left in a dark place for twenty minutes. It is then shaken again, and a specimen is taken out by a swab and rubbed onto the medium.

The first technique, though very simple, may cause more contamination if large inoculum is taken up on the swab. The second technique eliminates this fault and therefore it is simpler for the use of personnel not accustomed to bacteriologic work. However, due to dilution of the specimen, the number of positive results should decrease theoretically. In the writer's experience so far, there is no noticeable difference in the results with the two techniques.

Urine and gastric contents are prepared in a manner similar to the second method used for sputum. Larger specimen bottles are used. After adding oxalic acid solution, the mixture is allowed to sediment for thirty minutes. The supernatant liquid is decanted and the sediment is plated onto the medium by swabbing.

Pleural effusions are prepared in a similar way. However, treatment of the centrifuged specimen with oxalic acid and plating of the deposit is a more useful method.

Sterile pus from unruptured lymph nodes and the clot from cerebrospinal fluid may be plated directly onto the medium without previous preparation. If not sterile, oxalic acid should be used.

Incubation: The slopes are incubated at 37°C. The average growth time for *Mycobacterium tuberculosis* has been twenty days (range thirteen to forty-nine days). Delays of up to ten days have occurred between inoculations and incubation. In a tropical climate this delay did not appear to have affected growth materially. Contamination of inoculated medium during air transportation is avoided by screwing on the caps of the containers securely.

Evaluation: The slopes are inspected weekly. Contaminated slopes are discarded if contamination covers a large part of the surface of the slope, but are retained if only a few contaminating colonies are observed. It has been found that mycobacterial colonies later grow recognizably under these circumstances.

Cultures should be read by an experienced physician. There is little need for further examination by staining. The colonies are usually quite characteristic. Positive cultures are further examined by secondary cultures on drug-susceptibility slopes and two control slopes. One control slope is used later for the catalase-peroxidase test, the other is kept at room temperature. The secondary cultures are read after three weeks' incubation.

Records: Records are essentially simple. Primary cultures are recorded as negative or positive (+ for a few colonies, ++++ for complete cover of the slope). Drug susceptibility is recorded simply as susceptibility or resistance, and the dilution of the drug is noted. Room temperature growth is recorded as positive or negative.

Catalase-peroxidase testing: The reagent used is a freshly prepared solution of equal parts of 2 per cent catechol in distilled water and 20 volume hydrogen peroxide. Ten to fifteen drops of the reagent are placed onto the horizontal slopes. The results are recorded as follows:

C (catalase) + for the usual reaction for pathogenic mycobacteria
C++ for the usual reaction for saprophytes
C± for doubtful reaction
C− if no reaction is observed
Peroxidase reactions:
P+ if a well marked color change occurs
P± if the color change is just visible
P− if no change occurs

The methods of recording give enough information about a grown organism for the present purpose. If further examination is necessary, the primary growth can be sent to a fully equipped laboratory.

* * *

It is believed, as the result of the experience of the past nine months, that the modified Löwenstein-Jensen medium described can be used satisfactorily up to three months after preparation, and that concentration and neutralization of the specimen can be discarded under the conditions which prevail in field work in the underdeveloped countries. No attempt is made to compare the results with those of the classical methods. Unconcentrated and unneutralized material has been used in the Territory of Papua and New Guinea with success, giving 30 per cent more positive results than direct microscopic examinations. The buffering potential of the medium is sufficiently high to cope with all but very large amounts of inoculum.

This experience runs counter to customary recommendations which in the past may have been intimidating to workers in areas denied the facilities of first-class laboratories. The method described differs in respect of neutralization from a similar one described by Nassau, who uses potassium citrate for the neutralization of specimens.

The medium can be made with a minimum of equipment in a short time. The quantities described are given as a guide, and smaller and larger amounts can be made if desired. These quantities are sufficient to supply 240 thirty-milliliter bottles and 250 fifteen-milliliter bottles. Thirty-milliliter medium bottles were selected for primary cultures because they give a larger surface and better chance for growth, at the same time increasing the buffering potential of the medium.

Inoculation is simple and safe. The actual work needed in this method is less than that necessary for direct smears if large numbers of specimens are tested. It is believed that success is due to the fact that fresh specimens are inoculated without delay onto the medium. There is no doubt that the time lapse between the collection of the specimen and the inoculation is crucial and may lead to failure to grow the organism. For sputum examination the best results are obtained by using early morning specimens.

Oxalic acid was chosen for the reason that it is easier to handle and transport than sodium hydroxide or hydrochloric acid. Quaternary ammonium bases may well prove to be satisfactory but at the same time may have some inhibitory effect on growth if not washed out prior to inoculation. This introduces a complicating factor into a simple technique and may also imply added danger to staff. For these reasons the materials were rejected.

The susceptibility test dilutions, using only streptomycin, isoniazid, and PAS, may appear to be an oversimplification to the pathologist accustomed to more elaborate methods, and the recording of the results may be considered primitive. To those engaged in tuberculosis control on a mass scale who recognize the crudity of the susceptibility tests available to the writer and their real relevance to the management of the individual patient, and who are primarily concerned with drug resistance in its epidemiologic implications, the tests discussed are satisfactory. The tests distinguish between pathogenes and saprophytes, and between catalase-negative and -positive organisms.

It might be added finally that the medium can be used successfully to test the viability of BCG vaccine. Growth usually occurs in ten to fourteen days after inoculation.

In summary: A method for the culture of *Mycobacterium tuberculosis* has been described which can be used successfully in those areas where classical cultural methods are not feasible. The aim has been to develop a method which is suitable for use in the field where some delay may be experienced between the collection of the specimen and incubation, and which will reduce the possibility of contaminations to a minimum. The method met these requirements, and has been used successfully in the Territory of Papua and New Guinea in the past nine months.

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PRELIMINARY STUDY OF THE PILL CALENDAR AS A METHOD OF IMPROVING THE SELF-ADMINISTRATION OF DRUGS

In the past twenty to twenty-five years there has been a rapid increase in the number of effective therapeutic agents available to the medical profession. At least in part, many of these agents are given to the patient to be taken at home; under these circumstances the effectiveness of the drug may be limited by the inability of the patient to take the drug regularly as prescribed. This problem of self-administration of drugs is particularly important in situations in which the patient is essentially asymptomatic and yet is required to take drugs regularly for a long period of time. This occurs with the treatment of tuberculosis, the chemoprophylaxis to prevent recurrences of rheumatic fever, and the use of oral contraceptives.

Recently the seriousness of this problem has been studied by several investigators. A report by Ireland (Amer Rev Resp Dis, 1960, *82*, 378), based on careful records of the refills of medication in an outpatient clinic for 264 tuberculous patients who had been discharged from the hospital with medical consent, revealed that after twelve months of home treatment 26 per cent of the patients placed on ambulatory therapy did not return to the clinic for renewal of their drug supply. Forty-three per cent appeared to be taking none or less than 50 per cent of the drugs prescribed, and only 25 per cent were thought to be taking within 90 per cent of the medication as ordered. In Ireland's review of the literature he found that various investigators had studied the problem by testing the urine for evidence of PAS and found postive reactions for PAS in 25.5 to 75 per cent of the urines tested, most studies giving a value in the range of 50 to 60 per cent. In view of the fact that these studies revealed serious irregularity in the self-administration of drugs, it was deemed worth while to try new methods of drug administration.

Description of the pill calendar and rationale for its use: In attempting to assess why some people do not take medication properly, it was postulated that the main reason was simple forgetfulness. To combat this it was decided to place pills on a calendar and give the medication to the patient in this form rather than in a bottle. This device was labeled a pill calendar (figure 1). It was constructed by packaging the daily dose of medication in cellophane envelopes and stapling the envelopes to a 12- by 8-inch cardboard calendar. As isoniazid alone was the drug regimen employed, the daily dose was put in one package and the patient was instructed to take all of it every morning in sequence according to the calendar. He was further instructed to leave any forgotten doses of medication on the calendar. In addition to the monthly calendar full of pills, each patient was supplied with a wooden rack that could be hung in his dwelling in some easily visible place, to which the pill calendar could be attached.

It was believed that this device would promote regularity in the self-administration of drugs for several reasons. First, it would act as a reminder to the patient to take his medication regularly and, in addition, offer him some degree of psychologic gratification if he was able to keep a perfect or nearly perfect record. In the case of the sincere but forgetful patient, the forgotten pills that remained on the calendar would serve to bother his conscience and presumably stimulate him to do better in the future. Second, if the patient could not be relied on to take medication regularly, it should be possible to find other members of the family who would be interested in the patient's therapy, and the pill calendar hanging in an easily visible place offers an ideal way for the family to check on the patient. Finally, to some extent the pill calendar could serve as a means by which public health workers could supervise the patient by periodic surprise visits to the patient's home to see if the calendar was being kept properly. The limitations of this type of checking are discussed later.

Patient group: Twenty-nine Navajo patients attending the Navajo Cornell Field Health Research Project at Many Farms, Arizona, were chosen for study. All of them had been taking isoniazid from a bottle and were then changed over to a pill calendar for approximately three months. Patient regularity with the two methods of drug administration was compared by means of patient opinion, pill counts, and pill calendar checks. The patients were illiterate except for six school children and one adult; however in fourteen of the twenty-two homes where the patient was illiterate there was at least one member of the family who had been to school. The patients had been on outpatient therapy prior to the beginning of the study from one to forty-eight months, with an average of seventeen months. The patients were encouraged to return to the clinic monthly for a refill of pills but, because of the distance they lived from the clinic, up to 20 miles, and lack of anything but horse-drawn vehicles in the majority of instances, they had never returned regularly for refills, and it had been the policy to deliver the pills to the homes if the patients did not come in. Two-thirds of the medication refills were being made in this

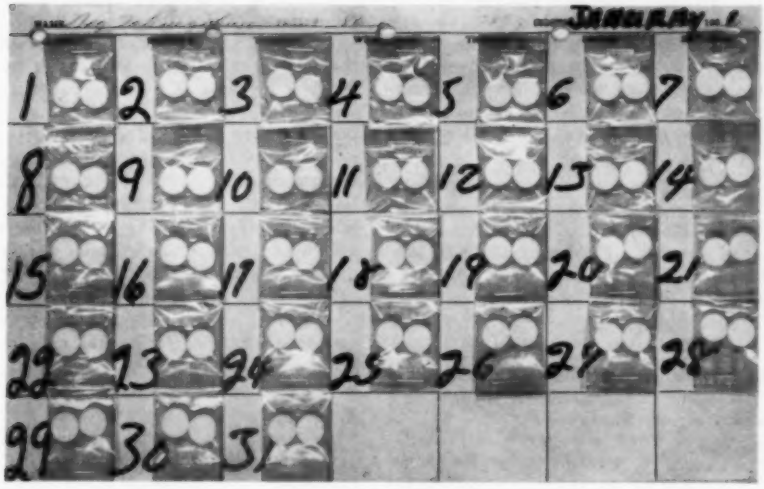

FIG. 1. Pill calendar.

manner prior to the beginning of the study, and so for purposes of the study it was decided to continue this policy of delivering medication.

Patient opinion of the calendar: At the completion of the study all of the patients (or, in a few instances, their families) were asked the question: "Did you do a better job of taking your pills from the bottle or the pill calendar?" Nineteen answered they did better with the calendar. Two stated they did no better on the pill calendar since they were perfect or nearly perfect on the bottle; but they liked the pill calendar. Four of the patients had had experience with the pill bottle for only one month or less so they could not make a fair comparison, but they all thought the pill calendar was a better method. One patient was neutral, admitting that he forgot frequently with both the pill calendar and the bottle. Three patients stated that the pill calendar was a hindrance and they preferred the bottle all for the same reason, namely, that they spent a great deal of time away from home and the pill calendar was hard to take with them. In sum, 25 of 29 patients were favorably impressed, one was neutral, and 3 disliked the new device.

Pill calendar checks: In order to assess further the effectiveness of the pill calendar device, Navajo subprofessional workers made periodic surprise visits to the patients' homes, examined the calendar, and marked the placement of the packages of pills on a blank calendar which was then brought back to the clinic for recording and analysis. At least one check was made each month and from four to eight checks were made per patient during the course of the experiment, with an average of 4.8 checks per patient.

It was realized from the onset that these calendar checks suffered from inaccuracies. The first of these would have occurred if the patient forgot to take his medication at a point in the month after the pill calendar check had been made, since at the end of the month the patients usually threw away their used pill calendars. In 41 of the 87 patient months of the experiment, the calendar check was made before the last week of the month, so that under-reporting due to this cause was probably present to some extent. Another source of error would have occurred if the patient, upon discovering that he had forgotten to take his pills, removed the pills and threw them away in order to avoid having the discrepancy discovered. Although this type of cheating undoubtedly occurred, the calendar checks appeared to show that at least part of the time the patients were honest.

Eighteen of the 39 groups of packages of pills left on the calendar were separated from the properly remaining packages by one or more spaces indicating that the patient had discovered the error and elected to follow instructions by returning to the proper package for that day, leaving the forgotten pills on the calendar. Both of these sources of error would tend to result in under-reporting of patient irregularity. This must be taken into account when the following figures are reviewed.

The pill calendar checks revealed that 13 persons had no forgotten pills remaining on the calendar, 13 persons had a total of one to seven forgotten packages remaining, and 4 persons had a total of eleven or more packages remaining during the duration of the experiment, approximately three months. The details are as follows:

Pills Improperly Remaining on the Pill Calendar during Three Months of Pill Calendar Usage

Number of packages remaining	0	1	2	3	4	5	6	7	11	12	13	32
Number of patients	12	4	3	1	1	1	2*	1	1	1	1	1

* One of these patients frequently had pills missing from the calendar and was thought to be considerably more irregular.

The checks also revealed discrepancies in the other direction, namely, packages missing from the calendar that should have been there on that date. On three occasions children in the house had removed several packages of pills from the pill calendar when the parents were not watching. On one occasion one package of pills had been lost because it was insecurely fastened. On three occasions the total count was correct, but the pills had been taken from the wrong place on the calendar. This occurred twice in the first month when apparently the patients did not completely understand the calendar. Since all of these errors were small, involving not more than one or two packages of pills, and since all pills that had been lost were replaced, these errors did not represent irregularity in self-administration.

However, there was one patient in whom this type of error, namely pills missing from the calendar, probably represented considerable irregularity. This patient had only two packages of pills improperly remaining on her calendar, but on four occasions she was found to be missing from 1 to 4 packages, a total of 9 altogether. The apparent explanation was that she traveled extensively, often being away several days at a time, and before leaving she would take several packages from the calendar and then frequently lose the detached packages. From her statements and those of her children we believe she was quite irregular, and so she was included in the group of unacceptably irregular patients described below.

Therefore, on the basis of pill calendar checks, 12 persons (41.4 per cent) had perfect records, 12 persons (41.4 per cent) had acceptable records (1 to 7 forgotten pills remaining on the calendar in three months), and 5 persons (17 per cent) were irregular to a greater degree and were arbitrarily designated as unacceptably irregular.

It is interesting to note that the results with pill calendar checks compared well with the results found by patient opinion. The 5 patients who were classified by calendar checks as being unacceptably irregular included all 4 of the patients who when questioned about the calendar were either opposed to it or neutral. The fifth patient classified as unacceptably irregular claimed that, although she was irregular on the calendar, she did far better with it than she did with the bottle; and considering the fact that only eleven forgotten packages were found on the calendar during the three months, this was probably true.

Comparison of previous record with pill calendar record: In the time prior to starting the patients on the pill calendar there was no system of pill counts to check on the self-administration of drugs. However, when the pill calendars were first given to the patients, the old pills were collected when possible. It became obvious in 6 instances that the patients had a great surplus of pills, a supply for three weeks to two months more than they should have had, and hence were grossly irregular in the self-administration of drugs. In addition, at the time the pill calendar was first given, one patient admitted he had taken very few pills in the preceding three months. Two of these 7 patients who were seriously irregular before using the calendar had perfect pill calendar records, 2 had acceptable records (2 and 5 packages found during the three months), and 3 remained unacceptably irregular.

Additional observations: Since one of the reasons why the calendar was supposed to work was so that the family could use the calendar to check on and remind the patient, it was decided to question the family and the patient about this matter. In 9 of the 31 cases the patient alone apparently took the sole responsibility for his medication, but in 20 cases the family participated. It was also considered that the stigma of tuberculosis might prevent the patient from hanging the calendar in a conspicuous place. This did not seem to occur, and in all but 2 of the cases the calendar was kept hanging in an easily visible place.

Finally, an attempt was made to see if literacy and school attendance were in any way correlated with the effectiveness of the calendar. The patients were placed into three groups: those who were in school or had been to school, those who had not been to school but a member of whose family had been to school, and those from families in which no one had been to school. According to the figures presented below, there is a suggestion of an increase in the regularity in self-administration of drugs when the patient was in, or had been to, school. However, it is interesting to note that, even among the 8 cases in which neither the patient nor any member of the family had been to

school, 2 had perfect records; 4, acceptably irregular records; and only 2 were unacceptably irregular.

Calendar Record	Perfect	Acceptably Irregular	Unacceptably Irregular
Patient had been to school	5	1	1
Patient had not been to school, but members of family had	5	7	2
Neither patient nor family had been to school	2	4	2

* * *

On the basis of admittedly crude and inadequate methods of testing there seems to have been an improvement in drug consumption while the patients took their medication from a calendar. However, it must be admitted that the patients were supervised to a much greater extent while using the calendar than they were at any time prior to using the calendar, and the apparent improvement may have been due to this alone. Therefore, it is recommended that the matter be explored further with a controlled pill calendar-bottle comparison study using urine testing to determine the degree of regularity, particular care being taken that both the calendar and bottle groups have equal amounts of supervision.

The fact that the patients did as well as they did despite that fact that in some families all members were illiterate may appear surprising, especially in the 2 cases in which perfect pill calendar records were maintained despite complete illiteracy in the home. Actually this is not so surprising when it is realized that in all Navajo homes, literate or illiterate, there is a regular American type of calendar which the people use in planning their attendance at social and religious events or at any form of business. Nevertheless, the fact that the calendar seemed to work in a setting of a semiliterate, semi-English speaking population is encouraging, and it might be expected that in a completely literate population it would work even better. However, with increase in literacy, there is usually also an increase in economic standards and, instead of living in one-room dwellings like the Navajo, multiple-room dwellings come into use. Under these circumstances the calendar would be less likely to be hung in a conspicuous place where all the family could see it, and hence might lose some of its effectiveness. It is also interesting to speculate whether, if the calendar were used for birth control pills, the patient would be willing to freely display it in her home.

The problem of how to use the calendar when the patient traveled was the most serious difficulty encountered and, if the patients' statements are correct, was the major cause of failure among the group of unacceptably irregular patients. This problem could probably be solved as long as isoniazid alone was being used. By stamping depressions in a plastic or cardboard sheet, a disposable, calendar-like device no larger than a wallet could be made which would be easily portable. However, such a small device would not be as visible to other members of the family; hence, part of the value of the calendar might be lost. Obviously, some compromise between large size for visibility and small size for portability would have to be made, as well as the possible use of devices of various sizes for different patients, depending on how much they travel.

The other problem encountered, namely, children's taking pills from the calendar, could probably be partially solved by judicious placing of the calendar high enough so that children cannot get at it and, in view of the fact that isoniazid is a relatively nontoxic drug, whatever increased risk occurs is probably justified. The other potential danger of the calendar is that a patient who discovers he has missed several days of medication might feel compelled to correct the situation by taking all of the forgotten medication at once. We do not know of this occurring during the three months of this preliminary study.

In summary: It is proposed that regularity of self-administration of drugs can be improved by substituting pills attached to a calendar for the customary bottle of pills that is given to the patient. On the basis of a preliminary study of three months, utilizing patient opinion and checks of the patient calendar as parameters of effectiveness, it appears that the calendar does improve the regularity of self-administered medication. It is suggested that the matter be studied further by means of a controlled comparison study of the bottle and calendar, utilizing urine testing for the drug to determine which group takes the medication best.

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THE HETEROGENEITY OF BCG

To the Editor of the American Review of Respiratory Diseases:

The literature on the usefulness of BCG vaccination for tuberculosis abounds in tests and observations which place the product at many points along a range of effectiveness from very high to low or nonexistent. Authors have claimed results that gradate from excellence to worthlessness, and their statements cover experience in both animal and man.

Out of this welter of diverse claims, three illustrative studies may be cited, and this for two reasons: (*1*) They represent opposite poles in result for, on one hand, they come from the group of studies which extoll the virtue of the product and procedure and, on the other, from the group which downgrades it to the point of throwing it into the discard; and (*2*) the strains used have now been applied in critical experiments in animals. They are presented in the manner of case or observation reports.

Observation 1. In the years from 1935 to 1938—at a time when but few well-controlled observations on the use of BCG had been reported—Aronson and his associates[1] set up a study in protection of Indian children against tuberculosis by this agent. The work centered in several reservations in Alaska and mid- and southwestern United States and was carried out in 3,024 children who failed to react to tuberculin. Vaccination occurred in 1,565 of these children while 1,459 who were "living in the same area and under the same conditions" were named as controls.

The BCG culture used chiefly had been obtained from the Pasteur Institute twelve or more years prior to its employment in this study. The two groups of children underwent annual medical follow-up which, at its minimum, included tuberculin testing and X-ray examination; at its maximum, physical examination as well.

At the end of three years, 6 of the vaccinated children and 59 of the controls showed roentgenographic lesions indicative of tuberculosis[2]; 3 of the vaccinated and 11 of the controls had died of this disease. Aronson and Palmer[3] analyzed the data at six years to find that 4 of the vaccinated and 28 of the control children had died from tuberculosis—a ratio of 1:7. Review of the mortality eleven years after the study began showed that deaths from tuberculosis stood at 6 and 53, respectively, for the protected and the nonprotected groups—a ration of 1:8.9.[4] The final survey of results came twenty years after the start of the vaccinations and brought the death figures to 13 in the vaccinated and 68 in the control groups, or a ratio of 1:5, which indicates that the protective influence of the vaccine began to wane after ten or eleven years.[5]

Observation 2. Other workers, however, have arrived at some very different conclusions. In 1949 Palmer and asociates[6] began observations and comparisons between vaccinated and unvaccinated persons in Puerto Rico. For this study the BCG vaccine was prepared and shipped fresh when needed by the New York State Board of Health Laboratories from a strain which had been obtained years earlier from the Pasteur Institute. A group of approximately 78,000 people was reported in these studies, 50,000 as vaccinees and 28,000 as controls.

At the sixth year[6] the vaccinees had contributed 93 cases of tuberculosis, (a case rate of 31) and the controls, 73 cases (a rate of 50). The authors concluded that BCG was about 31 per cent effective.

Observation 3. These same authors in the same paper[6] presented data collected from studies made in Georgia and Alabama in 1950. The vaccine for those studies was provided by the Tice Laboratory in Chicago from a strain of BCG that came originally from Calmette at the Pasteur Institute.[7] In this series of observations 16,913 subjects more than five years of age were vaccinated and 17,854 became control cases by means of random selection. Results at seven years revealed that 17 cases of tuberculosis had developed among the vaccinees and 28 among the control cases (approximately 1 per 1,000 and 1.5 per 1,000, respectively).

In both of these groups (observations 2 and 3) and after extensive statistical analysis, which included also the fate of tuberculin reactors in the communities involved (who, of course, did not

[1] Aronson, J. D., *et al.*: Amer Rev Tuberc, 1940, *42*, 651.

[2] Townsend, J. G. *et al.*: Amer Rev Tuberc, 1942, *45*, 41.

[3] Aronson, J. D., and Palmer, C. E.: Public Health Rep, 1946, *61*, 802.

[4] Aronson, J. D.: Amer Rev Tuberc, 1948, *57*, 96; 1948, *58*, 255.

[5] Aronson, J. D., *et al.*: AMA Arch Intern Med, 1958, *101*, 881.

[6] Palmer, C. E., *et al.*: Amer Rev Tuberc, 1958, *77*, 877.

[7] However, it has turned out that the Tice Laboratory laid this culture aside later for the one now processed there, which is distinctly more effective and is equivalent in potency to the best of the BCG strains.

participate in the protective measures), these authors concluded that "if all non-reactors had been vaccinated, the total number of cases in the study populations would have been reduced by 8 to 9%...." They therefore recommended virtual discontinuance of BCG vaccination.

How explain such widely different results among careful observers! Where must one seek the imponderables or the subtle factors responsible? Of these, the quality of the strain must certainly come in for consideration, as Dubos[8,9] pointed out editorially in recent years when he questioned the unity of cultures of BCG obtained from various sources and indicated (*1*) actual discrepancies between them and (*2*) the need for standardization. Methods for determining both the potency (virulence) and viability have now been worked out.[10, 11]

Cultures or strains of BCG require standardization or enumeration of viable bacilli before comparison can be made between them. Accurate methods now exist that make it possible to determine the numbers of viable bacilli in suspensions through the use of 2,3,5-triphenyltetrazolium chloride which, though water-clear in solution, is reduced to a red color by the enzymatic action of living cells.[12] This method enables one to prepare suspensions of various cultures so that each of them will contain approximately the same number of living bacilli. It provides foreknowledge of viability, whereas results from colony counting are available only after inoculation. The procedure can be duplicated at will.

With this tool, comparative studies have been made on BCG cultures from four laboratories in this country and five abroad. It turns out that the three strains which were used in the several observations cited at the beginning of this communication were among the strains so gathered for comparison.[13] Results from these comparative studies in animals may therefore be correlated with the results from the use of BCG in the clinical observations to which reference has been made.

The three strains used in the observations cited have thus been "put through the paces" in the laboratory, and the results provide data for comparison. For instance, animals vaccinated with a given (measured) dose of the Phipps strain (observation 1 above), kept thirty months, and then challenged with a given dose of virulent tubercle bacilli revealed a remarkable degree of protection[13] quite as did Aronson's Indian children in his clinical experiments with the same strain. In like manner the strain used by Palmer and his associates in Puerto Rico, mentioned in observation 2, when put into guinea pigs in the same dose-and-time relationships as the Phipps strain (observation 1), established a moderate degree of protection[13] and thus corresponded fairly closely to the clinical deductions of these authors from their vaccination of Puerto Rican people. Finally, cultures of the strain employed in Palmer's clinical studies among the people in Georgia and Alabama, as recounted in observation 3, led to comparable results when put into animals—namely, the worthlessness[13] in animals correlated well with the suggested abandonment of the practice in man.

So, in these three well set-up clinical observations on the use of BCG, results were excellent, fair, and worthless, respectively. In a series of experimental studies using the same three strains (among several others), the results corresponded closely: the strain that yielded excellent results in humans provided a high degree of efficacy in animals, and the strain deemed worthless in human relationships was certainly worthless in animals.

These well-controlled experimental projects correlate with clinical observations on BCG and leave no doubt that wide differences in cultures of BCG exist, and they explain, in part at least, the diverse claims that have been made in respect to the immunizing properties of what, until now, has been considered to be a product of uniform quality. It appears that BCG may no longer be called BCG unless its specific identity is mentioned and unless standards of potency and viability are determined and, once established, are followed meticulously.

The basis for these differences is under study. One approach to inequity in potency has revealed the fact that prolonged cultivation of two years or more with seven- or fourteen-day transfer to media containing fraction V bovine serum will modify the capacity of BCG cultures by partially restoring original properties possessed by the strain. By such procedures, the ultimate descendants of a BCG strain which produces no lasting protection develops the capacity to confer a rather substantial degree of immunity.[14]

It appears that there now exists sufficient knowl-

[8] DUBOS, R. J.: Amer Rev Tuberc, 1949, *60*, 670.
[9] DUBOS, R. J.: Amer Rev Tuberc., 1959, *79*, 80; 1957, *75*, 692.
[10] MELVIN, I. G., AND VANDIVIERE, H. M.: Amer Rev Tuberc, 1958, *78*, 83.
[11] VANDIVIERE, H. M., *et al.*: Acta Tuberc Scand, 1958, *36*, 205.
[12] WILLIS, H. S., *et al.*: Amer J Med Sci, 1960, *240*, 137.

[13] The strains of BCG referred to in observations 1, 2, and 3 above are identified in footnote 12 (*see* page 138 of reference) as BCG No. 3, No. 2, and No. 1, respectively. The results from the animal experiments with these strains are portrayed in this paper.
[14] Personal communication from H. M. Vandiviere.

edge and a rational basis for establishing a set of standards, principles, and procedures for production of antituberculosis vaccine. If these are established and followed, predictable results or a predictable degree of immunity could soon be provided. Obviously a good many factors would enter into such a set of standards. These would include: (*1*) minutiae in preparation of media, transfer of seed, and avoidance of exposure to light; (*2*) age of culture, which would be held constant; (*3*) equal opportunity for individual cellular multiplication so that the culture would be essentially homogeneous in metabolic activity and individual cell age; (*4*) determination of total viable cells in the suspension; (*5*) knowledge of potency and adherence to a predetermined level for each lot of vaccine; (*6*) titration of vaccines to standards known to provide a given degree of immunity, and (*7*) critical quantitative controls of preservation methods.

A board, committee, or agency to carry through on such a venture would render a real service in this controversial field of endeavor, for tuberculosis remains a scourge in the world today. Such regulation seems to be in order as a principle even though vaccination in this country will almost surely be confined to limited groups who are unduly exposed.

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February 24, 1961

CHEMOTHERAPEUTIC MANAGEMENT OF TREATMENT FAILURES AND RELAPSES IN PULMONARY TUBERCULOSIS

To the Editor of the American Review of Respiratory Diseases:

I have read with interest the Statement of the Committee on Therapy of the American Thoracic Society on "The Chemotherapeutic Management of Treatment Failures and Relapses in Pulmonary Tuberculosis." I realize that such a statement by a committee probably involves some compromises and that in many areas of the problem our knowledge is incomplete. But may I make one or two comments in the light of work on this side of the Atlantic?

1) In its introductory remarks, the Committee suggests that, in the management of previously untreated patients, the combination of isoniazid with streptomycin or PAS is now fairly standard. I think it might have been wise to emphasize that streptomycin is best given daily and that to give this drug two or three times a week with only one other companion drug would result in an important proportion of failures.[1] The dose of isoniazid in the British trial was 200 mg. daily. Whether the failure rate would have been any smaller with a higher isoniazid dose is uncertain, but it would be wise to assume an appreciable failure rate, as indeed is indicated by many less well controlled trials, unless the contrary is proved.

2) If rapid progression of the disease is taking place while the patient is under therapy, the Committee suggests that one or more new drugs should be substituted or added. If rapid progression is taking place under therapy, this makes it virtually certain that the patient's organisms are resistant to the drugs in use. It may be reasonable to add *two* other drugs likely to be mutually effective in preventing resistance, but to add only *one* drug to a combination to which the patient's organisms are already resistant is to invite the emergence of resistance to the added drug.

3) As regards the dosages recommended, I have already commented on the dangers of intermittent streptomycin combined with a single companion drug. Work in the United States has suggested that a daily dose of cycloserine of 1 gm., is likely to be more effective than 0.5 gm., but it is true that this carries a higher risk of toxicity.[2] Work in this department on tetracycline in combination with viomycin or isoniazid has indicated that a dose of 2 gm. daily is greatly inferior to 4 gm. in preventing drug resistance.[3,4] Our experience suggests that a dose of less than 4 gm. is largely ineffective. The individual dose should probably not be less than 2 gm. Tetracycline is a largely ineffective companion drug to pyrazinamide[5] and to ethionamide.[5] In the case of PAS, there is some indirect evidence to suggest that the individual dose of the drug should not be less than 5 gm.

I suspect that most of the points I have made would in fact be accepted by the Committee. I am sure that the statement will have a very wide influence in the world, and I am concerned that the Committee's views might be misinterpreted

[1] BRITISH MEDICAL RESEARCH COUNCIL: Brit Med J, 1955, *1*, 435.
[2] U. S. PUBLIC HEALTH SERVICE: Amer Rev Tuberc, 1956, *74*, 196.
[3] MURDOCH, J. M., AND STEWART, S. M.: Brit J Tuberc, 1956, *50*, 85.
[4] STEWART, S. M., *et al.*: *Brit Med J*, 1954, *2*, 1508.
[5] STEWART, S. M., *et al.*: Brit J Tuberc, 1957, *51*, 158.
[6] SOMNER, A. R., *et al.*: Brit Med J, 1959, *1*, 486.

for lack of the sort of detail which I have indicated.

JOHN CROFTON
Department of Respiratory Diseases & Tuberculosis
University of Edinburgh
Edinburgh, Scotland

March 15, 1961

LONG-TERM CONSEQUENCES OF ISONIAZID ALONE AS INITIAL THERAPY

To the Editor of the American Review of Respiratory Diseases:

In the December, 1960, number of the AMERICAN REVIEW OF RESPIRATORY DISEASES, the United States Public Health Service Tuberculosis Therapy Trials on "Long-Term Consequences of Isoniazid Alone as Initial Therapy"[1] pointed out in the Summary that "among patients who were bacteriologic successes at forty weeks . . . patients who had received isoniazid alone did as well as those who had received combined therapy" and that "there is some indication that patients who were still infectious after forty weeks of treatment with isoniazid alone had a less favorable prognosis than failures on combined tharapy."

I would like to make some remarks on these statements and on the study as a whole:

1) I think it would be better to exclude from the controlled groups at five years—as well from the bacteriologic failures as the bacteriologic successes—all deaths from nontuberculous causes, all cases of inactive disease when cultures for tubercle bacilli are not available, and all cases with activity unknown.

2) After this correction there would be 39, 8, and 18 bacteriologic failures and 68, 79, and 68 bacteriologic successes at our disposal instead of 49, 13, 27, and/or 101, 118, and 103, respectively.

3) The small number of patients in the group of bacteriologic failures certainly "limits the analysis of their long-term experience," but it would be logical to compare the results of the whole three groups, bacteriologic failures and bacteriologic successes together, because these results are representative—and can be statistically analyzed—of the results obtainable after a five-year-period by applying isoniazid alone in comparison with combined therapy. In this way there would be 107 patients in the isoniazid group: 62 persons with inactive disease and 45 persons with active disease, i.e., dead, or in hospital, or with active disease, i.e., 42 per cent of the isoniazid group. In the streptomycin-PAS group there would be only 30 per cent of deaths and/or in hospitals, or active diseases; in the isoniazid-streptomycin group, only 26 per cent. The difference between the isoniazid group and the isoniazid-streptomycin group is statistically significant on 5 per cent significance levels.

It is worth mentioning that the controlled combination of isoniazid daily and of streptomycin, 1 gm. twice weekly, is not a good combination of these two drugs, as shown elsewhere.[2] The dosage of isoniazid was different in the British study, 100 mg. of isoniazid *twice* daily, and in the United States study it was *150* to 300 mg. of isoniazid daily; but there was no indication *how* the doses were administered in the United States study. The reports in the *Review*[1,3-6] always indicated only "plus isoniazid, 150 to 300 mg. daily."

4) It seems to us that a percentage of 42 per cent of treatment failures after a period of five years is a very high one, considering that today we have the possibility of obtaining much better results with correct, combined drug therapy.

5) We think that it would be more correct not to emphasize at the end of an important paper like the one by the USPHS Tuberculosis Therapy Trials "decreased toxicity, convenience, and economy" for the "appropriate use of a single drug," but to point out clearly that in all cases of tuberculosis other than minimal and/or without cavity there is a clear evidence of better results with correct, combined therapy than with isoniazid alone.

6) Summing up, it seems to us that the interesting follow-up of the patients treated in 1952 clearly shows the superiority of a combined chemotherapy—imperfect as it was at the time—in comparison with isoniazid alone for patients like these treated in the aforementioned study.

E. JANCIK
Tuberculosis Research Institute
Prague, Czechoslovakia

February 10, 1961

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[1] U. S. PUBLIC HEALTH SERVICE TUBERCULOSIS THERAPY TRIALS: Amer Rev Resp Dis, 1960, *82*, 824.

[2] MEDICAL RESEARCH COUNCIL: Brit Med J, 1955, *1*, 435.

[3] MOUNT, F. W., AND FEREBEE, S.: Amer Rev Tuberc, 1952, *66*, 632.

[4] MOUNT, F. W., AND FEREBEE, S.: Amer Rev Tuberc, 1953, *67*, 108.

[5] MOUNT, F. W., AND FEREBEE, S.: Amer Rev Tu-Tuberc, 1953, *67*, 539.

[6] MOUNT, F. W., *et al.*: Amer Rev Tuberc, 1953, *68*, 264.

To the Editor of the American Review of Respiratory Diseases

We find ourselves in agreement with part, at least, of Dr. Jancik's comments, and our disagreement might be still less if we had made our intent clear.

There is, it seems to us, very general agreement that combined therapy is superior to single-drug therapy for all cavitary disease and for all far advanced disease. Proponents of this view, which we believe to be correct, have sometimes unwittingly given the impression that combined therapy is necessary for *all* cases. On the other hand, our own and other's evidence shows quite clearly that isoniazid alone equals combined therapy for minimal and moderately advanced noncavitary disease, as judged by the immediate response to therapy. In the report in question, we found that the five-year experience of those who respond initially to isoniazid alone is quite as good as those who reach a similar point on combined therapy.

We cannot agree with Dr. Jancik's desire to combine the failures and successes. We decided to divide the material after careful consideration. When the trial was initiated, the whole range of cases from the mildest to the most severe was included in each treatment group. From the immediate results, it was clear that isoniazid was not effective as *frequently* as combined therapy. By dividing each treatment group on the basis of its condition at forty-weeks, we found that, by and large, forty-week successes were five-year successes and, likewise, forty-week failures tended to be failures at five years. Further, there was little difference at five years by regimen among successes or among failures. If the groups had not been divided by their forty-week condition, the five-year results would simply have reflected the forty-week results.

Dr Jancik's difference with us appears to be chiefly one of emphasis. While he would have us "point out clearly, that in all cases of tuberculosis other than minimal and/or without cavity there is clear evidence of better results with correct combined therapy than with isoniazid alone," we would feel that this is already widely accepted and that attention needs to be directed to the evidence that for minimal and moderately advanced noncavitary disease, isoniazid alone is as effective as combined therapy.

Shirley H. Ferebee
Andrew Theodore
Frank W. Mount
Tuberculosis Program
Public Health Service
Department of Health, Education, and Welfare
Washington 25, D.C.

March 22, 1961

Books

DIE ASBESTOSE DER LUNGEN. Genese—Klinik—Röntgenologie. By H. Bohlig, G. Jacob, and H. Müller. Pp. 166, Georg Thieme Verlag, Stuttgart, 1960. Price, $15.70.

Although doomed to disappear in the not too distant future when less injurious synthetic products replace asbestos, pulmonary absestosis remains for the present a problem which increases in importance with the growth of industrial need for the product. This monograph provides a comprehensive review of the entire subject.

The first pages serve to remind us that asbestos was used as far back as ancient times. The authors then discuss the physical properties of the ore, the extreme fineness of which is of great importance to the technologist and the medical man, and the experiments *in vitro* and *in vivo* which, being rather conflicting, do not explain satisfactorily the pathogenic activity of the dust. Even examination of the pathology cannot completely answer this question. Fibrosis from asbestos dust is prevalent in the lower lobes and is often distinguishable from that of other pneumoconioses, particularly silicosis, by the absence of nodular formations. The curious asbestosis bodies which dot the whole of the parenchyma have a significant value in diagnosis; but other dusts such as graphite, talcum, and aluminum may cause similar formations.

The section on lung function is very short. The authors limit themselves to the older classical tests, the measurement of apnea and vital capacity; they do not include evaluation of the blood gases or study of the pulmonary circulation and vascular bed. No mention is made of bronchoscopy or lung biopsy, which sometimes provide aid in diagnosis.

The polymorphic features of the clinical signs become more marked when the asbestosis is complicated by other conditions. Two such complications are dealt with in particular: tuberculosis, which according to the statistics is so rarely a complicating factor that a certain antagonism is assumed between the two diseases; and cancer, which is the most frequent cause of death.

The entire subject of roentgenography in asbestosis is admirably covered in an excellent chapter which is illustrated with a hundred well-chosen films. The authors keep the classification of the German radiologist, Saupe, only as a provisional one. In fact, technical progress and better knowledge of the disease in its primary stages call for a new schematization which takes its pattern from that which was introduced at Sydney for silicosis. The problems of roentgenographic differential diagnosis are clearly stated.

Several pages are devoted to prophylaxis and legislation. The book then concludes with a detailed index and a very good bibliography of more than 650 references. Unfortunately, some recent publications have been omitted.

This useful monograph covers the actual present knowledge of asbestosis. It is well written and attractively presented. It will be welcomed by all medical men and specialists who are interested in industrial diseases.

CH. GERNEZ-RIEUX
Institut Pasteur de Lille
Lille, France

CURRENT THERAPY—1960. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn. Pp. 808, W. B. Saunders Company, Philadelphia, 1960. Price, $12.00.

In this new twelfth edition, a wide range of subjects in medicine is covered by a formidable panel of contributing physicians, many of whom are recognized authorities. Twelve consulting editors in appropriate medical specialties have supervised the compilation. In the current edition, Dr. Ralph Wayne Rundles succeeded Dr. Cyrus C. Sturgis as consulting editor in charge of hematology.

In line with avowed objective of the editor, the major emphasis is on therapy. The discussions are generally concise and clear. The therapeutic methods outlined, rather than a compilation of prevailing opinion in the pertinent literature, reflect the experience and prejudices of the contributing author. Treatment schedules, including drug dosages, method of administration, and possible side effects, are given in considerable detail. Operative indications and postoperative management are included when necessary. The use of instrumental approaches, such as esophagoscopy and bouginage, are covered in appropriate places. A special section on fluid and electrolyte imbalances might prove helpful in future editions. There is a supplemental incomplete roster of drugs, which lists the drugs by proprietary names, but includes the generic names. An elaborate table of pediatric dosages is included.

In the section dealing with chronic pulmonary emphysema, it seems to the reviewer that inordinate emphasis is placed on the use of steroids in treating bronchospasm, instead of stressing more intensive use of inhalation therapy with broncho-

dilators, especially with an intermittent positive pressure breathing unit. This reviewer shuddered to see meperedine (Demerol®) recommended two to four times daily for bronchospasm. Acetazolamide (Diamox®) is not mentioned as a therapeutic adjunct in cases of chronic respiratory acidosis.

In a book of this type, discussion of the pathophysiology of disease is either omitted or greatly curtailed. Consequently, the rationale of treatment is not usually correlated with basic mechanisms of the disease process. The absence of even limited references may frustrate efforts to evaluate the clinical studies upon which proposed therapeutic regimens are based. On the other hand, there is no doubt that the book admirably fulfills its primary objective, to be a well-organized and concise guide to the busy practitioner, spelling out authoritative therapeutic programs in detail. The text will have limited value to those with specialized fields of medical interest who are able to evaluate critically current literature without assistance.

David M. Roseman
New York, New York

The Modern Treatment of Asthma. With Special Reference to Gold Therapy. Second Edition. By L. Banszky. Pp. 175, John Wright & Sons Ltd., Bristol (Williams & Wilkins Co., Baltimore, exclusive U. S. agents), 1959. Price, $5.00.

In his preface to the second edition of this monograph, the author states that his reason for preparing a second edition is that during the nine years since the first edition was published some of the theories offered had become obsolete. While the reviewer has not read the first edition, it is difficult to imagine what theories were included in it which are not present in the second. While a historical review of the early theories of the mechanism of allergic reactions is of value to anyone interested in the field, there is a danger in this monograph for the less sophisticated reader because ancient and obsolete theories are not clearly distinguished from current ones.

The book is divided into eighteen chapters and an appendix. The first twelve chapters cover the historic and current theories of the mechanisms of asthma, diagnosis, symptomatic treatment of the asthmatic patient, and a variety of miscellaneous topics. The last six chapters and the appendix deal with gold therapy in the treatment of asthma.

A few of these chapters merit special comment. Chapter four, "Asthma and Tuberculosis," is a twelve-page discussion of the relationship between these two diseases, with interlacing of therapeutic considerations, such as the use of tuberculin in the treatment of tuberculosis, the use of gold in the treatment of both tuberculosis and asthma, and the deficiency of adrenal cortex as the underlying etiologic factor in both diseases. The chapter is summed up by the following paragraph, which serves the reader with a warning of more to come: "To sum up, treatment of the allergic manifestations may lead to their disappearance only if a desensitization is possible, but ... Unless the root condition—the tuberculinization of the organism—is remedied and the deficient adrenocortical function corrected, a permanent improvement cannot be expected. I believe this can be achieved by the use of gold in asthma." Shortly after, the author states his theory that the root cause of asthma is a form of old tuberculous infection "which gradually gave rise to secondary disturbances such as vagotonia and allergic sensitization."(!)

One third of this monograph is devoted to gold therapy in the treatment of asthma. The reviewer has had no experience in the use of gold in the treatment of asthma, nor have several allergists with whom the reviewer has discussed this after receiving the monograph for review. It is of interest and should serve as a warning that the use of gold in the treatment of rheumatoid arthritis is generally contraindicated in patients who have allergic backgrounds because of the high incidence of allergic reactions, mainly exfoliative dermatitis, in such patients. That this concern is justified is borne out by the author's figures, which report fifteen such cases (7.38 per cent) of 203 asthma patients treated with gold. Of these fifteen, seven, or 3.44 per cent of the total, were cases of "real erythroderma followed by exfoliation." Certainly, this finding alone should be enough to remove gold therapy from serious consideration in the treatment of asthma.

After an introductory chapter in which the therapeutic use of gold prior to the eighteenth century is discussed, it is stated that gold was first used as a curative medium for bronchial asthma in 1932 by Dudan, who believed in the tuberculous origin of asthma and insisted that gold salts only had effect on the asthmatic condition if tuberculous origin could be clearly demonstrated by positive von Pirquet tests. Then follows a chapter on the effect of gold, the language of which is vague and meaningless to one who is looking for scientific content. Typically, the chapter closes with the statement expressing "... the view—which is amply supported by clinical experience of many years standing—that gold salts can, in certain chemical combinations and in certain concentrations, be a valuable mobilizer of Nature's reserve forces and a powerful help in the fight against asthma."

The remainder of the chapters on gold therapy are equally unsatisfactory. There are no controls

receiving standard treatment, much less a double blind study. Thus, results are classified from "very good" to "no improvement" on the basis of the course following the institution of gold therapy.

The author quotes several European workers who used gold in the treatment of asthma, and reported good results in from 50 to 60 per cent of their patients. Again, there is no mention as to the selection of patients or the use of controls in these studies.

The last two chapters on antidote to gold poisoning and complications from gold treatment should make the reader even more reluctant to try this therapeutic agent in the treatment of asthmatic patients.

While this monograph may be useful as a review for an investigator interested in the use of gold in the treatment of asthma or other conditions, it is of little value to one interested in the general clinical management of the asthmatic patient.

MURRAY DWORETZKY
New York, New York

DISEASE AND THE ADVANCEMENT OF BASIC SCIENCE. Lowell Lecture Series of 1958. Edited by Henry K. Beecher. Pp. 416, Harvard University Press, Cambridge, Massachusetts, 1960. Price, $12.50.

Most of the twenty-one eminent scientists have approached the theme of the Lowell Lecture Series, "that some kinds of fundamental advances in science can be made only from the study of disease," by glancing back, and from their strategic vantage points lauded the concepts and extolled the triumphs of science over disease. Scholarly, authoritative, chronologic accounts have been given of the advances in the molecular, genetic, architectural, biochemical, nutritional, viral, neurophysiologic, and psychologic fields of man's understanding of himself and of the derangements brought about in him by his maladies. The hindsight has been myopic in only several instances. Left largely unheeded, however, has been the axiom, "don't glance back, your enemies may be overtaking you," for the premise is abundantly expressed that the enemy is static and forced by repetition to show his nature to the persevering investigator. Optimism is therefore replete in the chapters between Dr. Pauling's anxiety for the "deterioration of the pool of human germ plasm" and Dr. Dubois' concern about the "sickly progeny" that science might breed unless medical scientists in dealing with an ameboid enemy "take a long-range (foresighted) view of the consequences of their activities, lest they come to know the anguish that atomic physicists experienced as they watched the tragic effects of their scientific triumphs." This book is provocative, abundantly but diffusely factual, and expensive.

F. STEPHEN VOGEL
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BOOKS RECEIVED

CLINICAL DISTURBANCES OF RENAL FUNCTION. By Abraham G. White. Pp. 468, W. B. Saunders Company, Philadelphia & London, 1961, Price, $10.50.

NURSING IN TUBERCULOSIS. By Louise Lincoln Cady. Pp. 489, W. B. Saunders Company, Philadelphia & London, 1961. Price, $6.50.

METABOLIC EFFECTS OF ADRENAL HORMONES. Ciba Foundation Study Group No. 6. Edited by G. E. W. Wolstenholme and Maeve O'Connor. Pp. 109, Little, Brown and Company, Boston, 1960.

ADRENERGIC MECHANISMS. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme and Maeve O'Connor. Pp. 632, Little, Brown and Company, Boston, 1960. Price, $12.50.

THE AIR WE BREATHE. A Study of Man and His Environment. Edited by Seymour M. Farber and Roger H. L. Wilson. Pp. 414, Charles C Thomas, Springfield, Illinois, 1961. Price, $14.00.

MEDICAL ALMANAC 1961-62. Compiled by Peter S. Nagen. Pp. 528, W. B. Saunders Company, Philadelphia & London, 1961. Price, $5.00.

ESSENTIAL HYPERTENSION. An International Symposium. Edited by K. D. Bock and P. T. Cottier. Pp. 392, Springer Verlag, Berlin, Göttingen, Heidelberg, 1960.

ORTHOPAEDICS. By George Perkins. Pp. 975, University of London, The Athlone Press, London (distributed in the U. S. by Oxford University Press, New York), 1961. Price, $29.00.

American Thoracic Society

NOTICES

The following dates and locations of the next three annual meetings of the National Tuberculosis Association and the American Thoracic Society have been selected and approved:

1962—Miami Beach, Florida—May 20–24
1963—Denver, Colorado—May 12–16
1964—New York, New York—May 24–28

SCHEDULE OF LABORATORY REFRESHER TRAINING COURSES

September 11, 1961–April 13, 1962

The following is a schedule of laboratory refresher training courses which are to be offered by the Laboratory Branch of the Communicable Disease Center, Atlanta, Georgia, from September 11, 1961–April 13, 1962. Information and application forms may be obtained from the Laboratory Branch, Communicable Disease Center, U. S. Public Health Service, Atlanta 22, Georgia.

DATES	COURSES	DURATION *weeks*
Sept. 11–Oct. 6	Laboratory Methods in Medical Parasitology Part 1. Intestinal Parasites (800) Closing Date*: July 31, 1961	4
Sept. 18–29	Fundamentals of Virology (819) Closing Date: August 7, 1961	2
Oct. 2–13	Fluorescent Antibody Techniques in Streptococcus Grouping (860) Closing Date: August 21, 1961	2
Oct. 9–27	Laboratory Methods in Medical Parasitology Part 2. Blood Parasites (801) Closing Date: August 28, 1961	3
Oct. 23–Nov. 3	Fluorescent Antibody Techniques in the Public Health Laboratory (845) Closing Date: September 11, 1961	2
Oct. 30–Nov. 17	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases (820) Closing Date: September 18, 1961	3
Nov. 27–Dec. 1	Laboratory Methods in the Diagnosis of Rabies (826) Closing Date: October 16, 1961	1
Dec. 4–8	Bacteriophage Typing of Staphylococci (856) Closing Date: October 23, 1961	1
Jan. 8–Feb. 2	Laboratory Methods in Medical Mycology (815) Closing Date: November 27, 1961	4
Jan. 15–26	Laboratory Methods in the Diagnosis of Tuberculosis (855) Closing Date: December 4, 1961	2

DATES	COURSES	DURATION weeks
Jan. 29–Feb. 9	Laboratory Methods in the Diagnosis of Tuberculosis (855) Closing Date: December 18, 1961	2
Jan. 29–Feb. 9	Serologic Methods in Microbiology (941) Closing Date: December 18, 1961	2
Feb. 12–23	Laboratory Methods in the Study of Pulmonary Mycoses (817) Closing Date: January 2, 1962	2
Feb. 12–23	Fundamentals of Virology (819) Closing Date: January 2, 1962	2
Feb. 26–Mar. 16	Laboratory Methods in Medical Bacteriology (838) Closing Date: January 15, 1962	3
Mar. 5–9	Laboratory Diagnostic Methods in Veterinary Mycology (940) Closing Date: January 22, 1962	1
Mar. 12–30	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases (820) Closing Date: January 29, 1962	3
Mar. 19–23	Special Problems in Medical Bacteriology (839) Closing Date: February 5, 1962	1
Mar. 26–Apr. 6	Laboratory Methods in Enteric Bacteriology (850) Closing Date: February 12, 1962	2
Apr. 9–13	Laboratory Methods in the Diagnosis of Rabies (826) Closing Date: February 26, 1962	1
†	Laboratory Methods in the Diagnosis of Malaria (805)	1
†	Special Training in Virus Techniques (821)	2–4
†	Typing of *Corynebacterium diphtheriae* (842)	1
†	Special Problems in Enteric Bacteriology (851)	2
†	Phage Typing of *Salmonella typhosa* (852)	1
†	Laboratory Methods in the Diagnosis of Leptospirosis (853)	1–4
†	Serologic Differentiation of Streptococci (854)	2
†	Special Problems in Microbiology (942)	1–2

* Closing date for registraion

† Courses given by special arrangement only.

11TH ANNUAL INSTRUMENT SYMPOSIUM AND RESEARCH EQUIPMENT EXHIBIT

October 9–12, 1961

The Committee on Symposium on Recent Developments in Research Methods and Instrumentation will hold a symposium at the National Institutes of Health, Bethesda 14, Maryland, from October 9 through 12, 1961. For further information, write to James B. Davis, National Institutes of Health, Bethesda 14, Maryland.

AMERICAN THORACIC SOCIETY STATEMENTS

Some members have requested a list of the various statements from American Thoracic Society committees which have been published within the past few years. The following statements, which have appeared in the REVIEW, are listed below for ready reference:

Committee Statements—1956–1960

Committee on Therapy

Acceptable Standards in the Treatment of Tuberculosis—April, 1956
The Present Status of Skeletal Tuberculosis—November, 1956
Female Genital Tract Tuberculosis—March, 1957
A Statement on Cycloserine—June, 1957
A Statement on Pyrazinamide—June, 1957
Indications for Adjuvant Corticotropin and Corticosteroid Therapy in Tuberculosis—October, 1957
Recommended Standards for Home Care of Patients with Tuberculosis—October, 1958
The Role of BCG in the Prevention of Clinical Tuberculosis—July, 1958
Antimicrobial Therapy of Tuberculosis—October, 1958
The Open-Negative Problem—July, 1959
Drug Treatment of Pulmonary Tuberculosis (An Interim Report)—March, 1959
Chemotherapy of Extrapulmonary Tuberculosis in Adults—March, 1960
Treatment of the Adult Tuberculin Converter—March, 1960
Chemotherapeutic Management of Treatment Failures and Relapses in Pulmonary Tuberculosis—November, 1960
Bacteriologic Considerations in the Therapy of Chronic Suppurative Bronchitis and Bronchiectasis—November, 1960
The Use of Corticosteroids in the Treatment of Sarcoidosis—November, 1960
The Use of Aerosolized Medication in Pulmonary Diseases—November, 1960
The Use of Respirators in the Treatment of Chronic Pulmonary Emphysema—November, 1960
The Use of Dihydrostreptomycin in Tuberculosis—November, 1960
Tuberculosis Control Programs for Nurses, Nursing Students, and Hospital Personnel—December, 1960

Committee on Respiratory Diseases in Children

Treatment of Tuberculosis in Children—March, 1960

Committee on Radiation Effects

The Chest Roentgenogram and Chest Roentgenographic Surveys Related to X-ray Radiation Effects and Protection from Radiation Exposure—July, 1959

Committee on Diagnostic Skin Testing

Homologous Serum Jaundice—January, 1960

1962 ANNUAL MEETING OF THE AMERICAN THORACIC SOCIETY

Invitation

The Medical Sessions Committee *INVITES SUBMISSION OF PAPERS* on all scientific aspects of tuberculosis and nontuberculous respiratory and cardiopulmonary diseases for presentation at the *1962 ANNUAL MEETING IN MIAMI BEACH, FLORIDA, MAY 20–23.*

Abstracts

(*1*) Abstracts of papers to be offered for presentation should be submitted before *JANUARY 5, 1962* to the Chairman of the Medical Sessions Committee. *EIGHT COPIES* are required for distribution to committee members, the first copy on bond and the remaining seven on onion skin. Abstracts of papers from investigators outside the United States will be most welcome provided they are in English and are submitted with the understanding that all papers accepted must be presented in English at the annual meeting.

(*2*) Abstracts should be limited to a 300-word summary including *IMPORTANT DATA AND CONCLUSIONS*, and should be typed double-spaced on a 60-space line. Charts and tables should be attached to aid in the selection of papers. Abstracts selected for presentation at the Annual Meeting will be published in THE AMERICAN REVIEW OF RESPIRATORY DISEASES. Manuscripts should be double-checked for accuracy before submitting.

(*3*) Reports of interesting or unusual cases will be considered for inclusion in case conferences.

(*4*) The names, most important academic degree, and title (*list only one*), and complete addresses of the senior author and co-authors should be included in each abstract.

(*5*) All abstracts will be reviewed by the Medical Sessions Committee. Selection will be largely based on the areas of interest suggested by you and others receiving this invitation.

(*6*) Authors will be notified by *FEBRUARY 5, 1962*, if their papers have been accepted for presentation.

(*7*) Papers presented at the Annual Meeting must be *ORIGINAL* contributions *NOT PREVIOUSLY PRESENTED OR PUBLISHED*. Medical papers presented at the meeting may be submitted to THE AMERICAN REVIEW OF RESPIRATORY DISEASES by the author if he so desires.

Suggestions

The Medical Sessions Committee is particularly anxious to build the 1962 program around your special interests. A memorandum suggesting subjects and speakers would be welcome and should be sent to the Chairman by *SEPTEMBER 25, 1961*.

Asher Marks, M.D., *Chairman*
Medical Sessions Committee
American Thoracic Society
1790 Broadway
New York 19, New York

THE AMERICAN REVIEW
OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

ABSTRACTS

Edited by EDWIN D. KILBOURNE

VOLUME 84 July 1961 ABST. NO. 1

The Editor recognizes the inevitable incompleteness and arbitrary selectivity of any abstracting service, including this one. It is his belief that the usefulness of the present Abstracts section will be enhanced if the reader is informed of the general purpose of the abstracts and the criteria employed in their selection.

It is the purpose of the Abstracts section to acquaint the diversified and international readership of the REVIEW with the gist of original and scientific articles which are related to the general subjects of tuberculosis or respiratory diseases implicit in the title of the journal. In this connection, 40 abstracters systematically review 239 journals which represent 36 countries and which are published in 22 languages. In most instances, abstracters cover journals in fields of their special competence. It is evident that the diverse interests of the readers of the REVIEW dictate a balanced selection of clinical, laboratory, and epidemiologic studies. Such selection will often preclude the publication of articles equal in scientific merit to many presented here.

In the publication of abstracts, cognizance is taken of the extent to which the journals yielding them are circulated. Articles from journals of wide circulation may be mentioned by title only. This space-saving device is also employed for articles which defy condensation without the omission of essential data or discussion. The attention of readers is thus directed to the existence of papers which are no less important because they are not summarized.

(Requests for further information on abstracted articles should be directed to the author of the article at the address indicated by an asterisk (*) in each abstract title.)

ABSTRACTERS

HANS ABELES, M.D., New York, N. Y.
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NONTUBERCULOUS THORACO-PULMONARY DISEASE

Studies of Pulmonary Alveolar Microlithiasis and Pulmonary Alveolar Proteinosis. E. P. Taxay*, R. D. Montgomery, and D. M. Wildish. *Amer J Clin Path*, December, 1960, 34: 532–545. (*U. of Miami, Fla.)

A case of pulmonary alveolar microlithiasis and a case of pulmonary alveolar proteinosis in West Indian patients are described. A course of therapy with a chelating agent produced no roentgenographic improvement in alveolar microlithiasis. The pathology of these diseases is briefly reviewed, and the possible interrelations of pulmonary alveolar microlithiasis, pulmonary alveolar proteinosis, and pulmonary corpora amylacea are discussed (after authors' summary).—E. Dunner

Pulmonary Alveolar Proteinosis with Unusual Complicating Infections. A Report of Two Cases. C. C. Jones*. *Amer J Med*, October, 1960, 29: 713–721. (*U. of Kansas Med. Center, Kansas City)

The clinical and pathologic findings are presented of 2 additional cases of pulmonary alveolar proteinosis, with further characterization of the alveolar lesion. Both patients presented lesions typical of pulmonary alveolar proteinosis. The first patient possibly had the disease over a 7-year period. The other had symptoms for only a few months. Both patients had dyspnea, slight cyanosis, clubbing of the phalanges, and pleuritic chest pains; both progressed to marked debilitation and died with superimposed infections. The proteinaceous material, when present for a number of years, may form large acicular crystals of undetermined nature which appear to excite granulomatous reactions in the surrounding alveolar walls. There is fibroblastic growth along crystal margins, and eventual fibrous organization of the involved alveoli. The presence of phospholipid as an additional constituent of the proteinaceous material may be indicated by its affinity for luxol blue stain. Roentgenographic changes suggesting pulmonary fibrosis were confirmed by histologic examination. It is suggested that fibrosis may be part of the evolution of the lesions of alveolar proteinosis, apart from the fibrosis caused by intercurrent infection.—T. H. Noehren

The Anomalous Origin of the Right Main Bronchus from the Esophagus. J. L. Keepey* and A. E. Schairer. *Ann Surg*, November, 1960, 152: 871–874. (*South Shore Hosp., Chicago, Illinois)

A newborn is reported who had esophageal atresia and a tracheoesophageal fistula with origin of the right main bronchus from the esophagus. Surgery performed on the fourth day of life was complicated by inability to expand the right lung. The patient died in the early postoperative period. Postmortem examination revealed that the right main bronchus arose from the esophagus, which explained the problems in expanding the right lung at the operation. This appears to be the first report of a main bronchus arising from the esophagus.—M. J. Small

The Use of Trypsin Given Orally in Chronic Bronchitis. Clinical and Functional Observations (in Italian). G. Camerota* and S. Di Pasquale. *Ann Med Sondalo*, No. 4, 1960, 8: 232–239. (*Villaggio Sanatoriale, Sondalo, Italy)

The clinical pathology of chronic bronchitis is particularly characterized by cough with sputum, which sometimes causes serious complications to the respiratory apparatus and to the circulatory system: any therapy in this field should aim to alleviate this symptom. The present small-scale study was done to learn if trypsin, given orally, is useful in controlling coughing. Thirteen patients, 40 to 60 years of age (8 with chronic bronchitis, 4 with chronic bronchitis and bronchiectasis, and 1 with bronchial asthma) were given 20 mg. of trypsin orally in 4 doses daily for a period of about 4 months; antimicrobial treatment was also continued. Clinical, functional, and laboratory tests were performed prior to and 15 days after the proteolytic substance was discontinued. Results were rapid and good: a decrease in coughing together with more effective expectoration were observed, with subsequent improvement of the general condition and respiratory function of the patient. Pulmonary function tests showed a good degree of improvement in respiratory efficiency, with an increase in vital capacity and air velocity, and a decrease in dead space.—I. Archetti

Lung Cancer in Women. K. Boucot* and H. Percy. *Dis Chest*, December, 1960, 38: 587–598. (*Woman's Med. College of Pennsylvania, Philadelphia)

The 5-year survival rate for 102 proved cases of lung cancer in women was 3 per cent. Only 1 woman was asymptomatic. Age distribution, symptomatology, and resectability were not unlike those reported in men. A striking difference between the sexes was the fact that only ⅓ of the cancers in women were of the squamous-cell type, compared with reported incidences of 50 to 60 per cent in men. The resection rate was 27 per cent, about the same as that for men. Only 1 woman had concomitant proved active tuberculosis, and 4 per cent had diabetes mellitus.—E. A. Rouff

Serum Enzymes in Bronchogenic Carcinoma and Other Pulmonary Diseases. J. GOLD*. *Dis Chest*, January, 1961, 39: 62–67. (*State U. of N.Y. College of Med., Brooklyn, N.Y.)

Elevated serum transaminase (SGO-T) and lactic dehydrogenase (LDH) have been reported in patients with neoplastic disease. Their diagnostic value in tumors of the lung as well as changes following roentgen therapy or resection was investigated. Eighty-two per cent of the patients with proved bronchogenic carcinoma were found to have elevated serum LDH. Patients with acute pneumonia also showed elevated values, with return to normal following resolution. Following resectional surgery the serum value returned to normal; thus, the test is believed to be of prognostic value in such instances. Normal values appeared in a majority of the cases treated with radiation or chemotherapy. The serum transaminase was found to be of no particular value in the diagnosis of bronchogenic carcinoma.
—E. A. ROUFF

Aberrant Forms of *Coccidioides Immitis* in a Coccidioidoma. A. G. SMITH* and J. P. GILLOTTE. *Amer J Clin Path*, November, 1960, 34: 477–487. (*U. of Maryland School of Med., Baltimore)

A review of the literature pertaining to the finding *in vivo* of mycelial forms of *Coccidioides immitis* reveals that such forms have been observed in 59 per cent of coccidioidal cavitations and in 24 per cent of coccidioidomas. A case history is presented involving recrudescent pulmonary coccidioidomycosis in which 1 of 2 coccidioidomas was observed to contain a wide variety of aberrant forms of the organism, including bead-like chains, nodular forms, yeast-like forms, and hyphal forms. The hematoxylin and eosin stain is inadequate for demonstrating the histopathology of coccidioidal infections. Both the periodic acid-Schiff and the methenamine-silver techniques are highly efficient, but the latter is superior for microscopic scanning. The desirability for cultural evidence of etiology is emphasized because of similarities that exist in the histopathology of several mycotic diseases.—E. DUNNER

Cryptococcosis: A Case Report. T. HAUSER*. *Ann Intern Med*, October, 1960, 53: 816–822. (*North Mesa Med. Group, Carlsbad, New Mexico)

A 56-year-old man developed a severe, acute, cryptococcal meningoencephalitis and, despite amphotericin B therapy, died 27 days after the onset of the illness. This case was one of pulmonary cryptococcosis of an estimated duration of several years, with a terminal spread to the central nervous system, producing severe meningoencephalitis.
—T. H. NOEHREN

Dysphagia Lusoria Presenting as a Superior Mediastinal Syndrome. R. MORRIS*. *Brit Med J*, November 26, 1960, No. 5212: 1558–1562. (*Johannesburg, South Africa)

A case of adult dysphagia lusoria due to an aberrant right subclavian artery compressing the esophagus is described which presented as chronic superior mediastinal compression. Complete disappearance of the symptoms and signs occurred after surgical resection. This is the first known instance of surgical treatment for the condition in an adult.—E. A. RILEY

Investigation of Unexplained Pleural Effusions in Africans. R. PAUL*. *Tubercle*, December, 1960, 41: 430–434. (*Pneumoconiosis Medical & Research Bureau, Kitwe, Northern Rhodesia)

Forty-two African adults in Northern Rhodesia who had unexplained pleural effusions were followed up for 2 to 10 years; only 2 (5 per cent) developed pulmonary tuberculosis. Of 17,697 mine workers who were tuberculin tested (Heaf test) and examined roentgenographically, 2,104 (11.9 per cent) had pleural thickening; of these, 16.5 per cent had negative tuberculin reactions. The pleural fluid was examined in 47 cases. Tubercle bacilli were cultured in only 17 per cent, and the cellular content was predominantly lymphocytic in only 64 per cent. There thus appears to be doubt of the validity of the widely held opinion that the majority of pleural effusions in Africans are tuberculous. As yet, no other specific etiologic factor has been discovered but, in view of the number of tropical infections prevalent in this African population, investigations will be directed along that line.—M. J. SMALL

Significance of Small Pleural Effusions in Cardiopulmonary Disease, and Some Other Observations on Pleural Fluid in General. L. CARDON*. *Ann Intern Med*, October, 1960, 53: 765–795. (*Northwestern U., Chicago, Ill.)

A relatively small pleural effusion, in the presence of antecedent cardiac and pulmonary disease which already seriously interferes with pulmonary function and causes difficulty in breathing, may precipitate a critical degree of dyspnea and air hunger, and may even cause death. An effusion of as little as 500 ml. may be significant in this regard. This situation occurs most commonly in middle-aged or elderly individuals with coexistent congestive heart failure and pulmonary emphysema or fibrosis, but a summation of other pathologic processes in the lungs (infarction, pneumonia, atelectasis, et cetera) in the presence of heart disease or failure may similarly enhance the final asphyxial effect of a small increment of pleural fluid. Recognition and mechanical removal of a small

pleural effusion by thoracentesis provide great palliative benefit, and are frequently life-saving.
—T. H. Noehren

Factors in the Development of Respiratory Insufficiency in Cystic Fibrosis. G. Polgar* and G. J. Barbero. *Amer J Dis Child*, November, 1960, 100: 733–734. (*Children's Hosp., Philadelphia, Penn.)

In the course of the pulmonary disease in cystic fibrosis of the pancreas, a certain periodicity is evident; episodes of severe pulmonary insufficiency alternate with intervals of relative freedom from symptoms. The final attack may be among the first, or may conclude a long series of similar exacerbations. In trying to understand these episodes, even the therapeutic program requires examination. During the serious episodes of the respiratory condition, therapeutic attempts are usually concentrated on physical respiratory aids—antimicrobial therapy, aerosols, and other means used to mobilize the mucus and enhance alveolar ventilation. Some of these methods, such as intermittent positive pressure breathing (IPPB) and oxygen therapy, may have certain dangers in routine use. Among these patients, 9 received a combination of IPPB and oxygen therapy with aerosol medication. Six died who had received this treatment mostly in the final episode. Three of the patients who survived have severe impairment of lung function in spite of similar treatment for up to 2 years, while 2 of this group did not receive it. None of the 5 who have only minor symptoms were treated with IPPB or oxygen inhalation. The question is raised whether such therapeutic efforts may contribute to other factors which turn one of the usual relapses of the respiratory disease into a fatal one.—M. J. Small

Pulmonary Changes in Acute Glomerulonephritis in Childhood. A. Holzel* and J. Fawcitt. *J Pediat*, November, 1960, 57: 695–703. (*St. Mary's Hosp., Manchester, England)

During a 3-year period (1954 to 1957), each of the 40 patients with acute glomerulonephritis who were admitted to Booth Hall Hospital for Sick Children, Manchester, was submitted to roentgenographic examination of the chest. Twenty-five were found to have definite lung changes. Of an additional 25 patients with nephritis who had been examined roentgenographically during the 5-year period from 1949 to 1954, 12 had roentgenographic findings similar to those in the original group studied. Segmental or lobar collapse, consolidation, intrapulmonary edema, and pleural effusions were the lesions encountered. They appeared in the first week of the illness and cleared with the onset of diuresis. The majority of these children had some degree of hypertension. There was no correlation between the age of the patient and the degree of azotemia present. The pathogenesis of the lesions, if there is a single etiology, is undetermined. The hypothesis is presented that the pulmonary changes are related to alterations in the extracellular fluid volume. However, in certain of the roentgenographic illustrations, the possibility of inflammatory changes cannot be eliminated.
—M. J. Small

Idiopathic Pulmonary Hemosiderosis. M. Yettra*, E. Goldenberg, and H. Weiner. *Calif Med*, December, 1960, 93: 330–336. (*Kaiser Foundation Hosp., Los Angeles, Calif.)

Two more cases of this rare condition are reported in detail. The symptoms in both adults and children are recurrent pulmonary hemorrhages, cough, diffuse roentgenographic abnormalities, and moderate to severe hypochromic anemia. The clinical course is characterized by remissions and exacerbations. The anemia may improve spontaneously, but the roentgenographic changes never return to normal even though acute massive infiltrations may partially resolve. The diagnosis is confirmed by iron stains of the sputum or by lung biopsy. Correction of the anemia by intensive iron therapy and transfusion is an important part of therapy. Splenectomy and corticosteroids have been utilized with no definite conclusions being drawn from their use.—E. A. Rouff

Idiopathic Respiratory Distress Syndrome of the Newborn: An International Exploration. A. J. Rudolph* and C. A. Smith. *J Pediat*, December, 1960, 57: 905–921. (*Box 7242, Johannesburg, South Africa)

An informal discussion of hyaline membrane disease (idiopathic respiratory distress syndrome) was held on July 21, 1959, at the IX International Congress of Pediatrics in Montreal. This paper is an edited tape-recorded typescript of that discussion. An attempt was made to clarify what different clinics mean by hyaline membrane disease, respiratory distress, pulmonary syndrome, and other terms. This international group also tried to make some clinical assessment of severity so that workers from various places could more accurately compare their data, especially as to treatment. In a final summation of opinion, it is of interest that 15 of the participants thought the preferred diagnostic term for this condition should be "idiopathic respiratory distress of the newborn." Four conferees voted for the term "pulmonary syndrome of the newborn," and only 3 for "hyaline membrane syndrome."—M. J. Small

The Relationship of Fatal Pulmonary Insufficiency with Cor Pulmonale, Rightsided Mural Thrombi and Pulmonary Emboli: A Preliminary Report. G. L. Baum* and F. D. Fisher. *Amer J Med Sci*, November, 1960, 240: 609–612. (*V.A. Hosp., Cincinnati, Ohio)

Previous reports of acute cardiopulmonary failure in patients with severe chronic pulmonary insufficiency due to emphysema have not emphasized the role of right-heart mural thrombi and pulmonary emboli in the genesis of the terminal syndrome. Absence of the usual signs of infection has been a recognized inconsistency in some patients with acute cardiorespiratory failure supposedly due to infection; this has been shrugged off as a peculiarity of the disease. The necropsy protocols were examined of patients who were found to have pulmonary emphysema, cor pulmonale, right-heart mural thrombi, or any combination of these conditions. In a total of 1,135 necropsies, 39 patients had one or more of these entities as their major symptom; 33 had pulmonary emphysema; 30 had cor pulmonale and, of these 30, 28 had pulmonary emphysema. In 9 instances, multiple pulmonary emboli and rightsided mural thrombi were associated with fatal pulmonary insufficiency and cor pulmonale. The findings suggest that acute cardiorespiratory insufficiency with carbon dioxide intoxication, although of uniform clinical pattern, may have either a primarily infectious or primarily embolic pathogenesis. When pulmonary emboli are small, the effect is not catastrophic. Further physiologic studies on patients with pulmonary emphysema, utilizing more precise techniques in attempts to determine the presence or absence of pulmonary emboli, may well reveal a difference in pattern between those patients in whom the acute cardiopulmonary insufficiency is essentially infectious as opposed to those in whom the insufficiency is vascular or embolic in origin. The possible use of anticoagulants in selected patients with this syndrome is suggested.—W. J. Steininger

A Three-Step Method for the Diagnosis of Solitary Pulmonary Nodules. L. H. Garland*. *Canad Med Ass J*, November 19, 1960, 83: 1079–1082. (*U. of California Med. School, San Francisco)

Utilizing a 3-step method involving roentgenographic studies, clinical data, and laboratory tests, it was possible to classify as presumptively "benign" or "malignant" 106 of 115 consecutive solitary pulmonary nodules. Of the 68 nodules diagnosed as benign, 66 were verified; in 2, a mistake was made—the studies proved to be primary malignant tumors. Of 38 cases diagnosed as malignant, 34 were verified and 4 proved to be benign lesions (1 benign tumor, 3 granulomas). Of the 9 unclassified nodules, 5 proved to be malignant tumors and 4, benign lesions (3 granulomas and 1 benign tumor). In the entire group of 115 solitary nodules, 74 were benign lesions, of which 66 were correctly classified by the 3-step method (89 per cent). Malignant lesions numbered 41, and 34 of these had been correctly diagnosed (83 per cent). The malignant lesions included 2 solitary metastatic lesions and 39 primary bronchial carcinomas.—E. A. Riley

Chronic Suppurative Pneumonia (in Hungarian). G. Meszaros*. *Tuberkulozis*, June, 1960, 6: 170–173. (*U. of Debrecen, Hungary)

This entity is an inflammatory disease of the lung (synonym: primary chronic pneumonia) of unknown etiology which manifests as a parenchymatous lesion of one or more lobes of one lung. It may be present for a long period of time, sometimes several years. Among 37 patients observed, 26 were treated with surgical resection, which is the recommended procedure if intensive treatment with antimicrobials is not effective in 6 to 8 weeks. —Z. Virágh

Tuberculosis and Asthmatic Bronchitis in Sarcoidosis. H. Ten Have* and N. Orie. *Dis Chest*, January, 1961, 39: 42–79. (*State U., Groningen, Netherlands)

A group of 150 patients of some 700 with sarcoidosis were analyzed for significant characteristics on the basis of severity. The most striking findings were the high frequency of contact with proved active tuberculosis, the evidence of calcification during the course of the disease, the high frequency of asthmatic bronchitis in cases of diffuse long-standing third-stage lesions, the relatively low incidence of respiratory infections, the favorable effect of corticosteroids symptomatically and anatomically, and the unfavorable prognosis in cases with iridocyclitis. The over-all mortality rate was 2 per cent, with serious sequelae occurring in 6 to 10 per cent of the cases.—E. A. Rouff

TUBERCULOSIS, PULMONARY

"Atypical" Mycobacteria in Sanatorium Patients, Hospitalized with the Diagnosis of Pulmonary Tuberculosis. Ij. N. Oosterbaan*. *Proc Tuberc Res Council* (Netherlands), No. 46, 1959: 89–105. (*Sanatorium Hornerheide, Horn, Netherlands)

Since about 1950, unclassified (atypical) mycobacteria have been demonstrated in patients with lesions (mostly pulmonary) which could neither roentgenographically nor histologically be distinguished from tuberculosis. An etiologic con-

nection between the unclassified microorganisms and the pulmonary lesions is now generally accepted. A short survey of the pertinent literature is given. A number of patients are reported; they were admitted to the sanatorium during the years 1956–1958 with the diagnosis of pulmonary tuberculosis, but unclassified mycobacteria were demonstrated in their sputum or other specimens. It is striking that none of the patients was younger than 20 years. In previous studies, unclassified mycobacteria were never demonstrated in patients with lesions which were roentgenographically regarded as primary lesions. It is noted that no source of contamination could be established for any of the cases. Nearly all of the patients came from nontuberculous families. Localization of the lesions in the right upper lobe was practically the rule in this case material. Drug treatment offers only limited possibilities; this tallies with the results of the drug-resistance tests. As extension of the lesions may signify a grave prognosis, resection was often considered indicated in these cases. Finally, it is noted that in this series photochromogens were predominant; unclassified mycobacteria other than photochromogens were encountered in one case only. The author's impression, if only preliminary, is that in the region concerned (the province of Limburg) photochromogens are the preponderant type of unclassified mycobacteria (taken from English summary).

Chronic Cor Pulmonale in Pulmonary Tuberculosis (in Italian). G. Mazzei*. *G Ital Tuberc*, No. 4, 1960, 14: 226–237. (*Villaggio Sanatoriale, Sondalo, Italy)

Forty-two cases of chronic cor pulmonale were observed in patients with pulmonary tuberculosis. Most of the cases (45 per cent) were in persons between 40 and 50 years of age and only 5 (11 per cent) were found in persons less than 30 years of age. In 48 per cent of the cases, the pulmonary disease had lasted for more than 5 years. The clinical manifestations and the roentgenographic and laboratory data are described. Electrocardiographic examination is particularly emphasized as a means of diagnosis, and the main electrocardiographic patterns observed in this study are given. Finally, it is stated that uncomplicated pulmonary tuberculosis, even if very diffuse, does not cause right heart overwork, but when the tuberculosis is associated with emphysema or diffuse pleural fibrosis it easily induces chronic cor pulmonale.
—I. Archetti

A Study of Gustatory and Olfactory Sensitivity in Patients with Pulmonary Tuberculosis (in Portuguese). V. Lorian*. *Rev Bras Tuberc*, December, 1960, 206: 373–376. (*Bucharest School of Med., Roumania)

A study was organized to demonstrate the actual state of gustatory and olfactory sensitivity in patients with pulmonary tuberculosis. The study employed 160 tuberculous patients, 20 patients with pulmonary cancer, and 30 patients with pulmonary abscess. The results were that 71 per cent showed normal reactions to acid solutions while 29 per cent showed only minute changes; 62 per cent were normal in sensitivity to salty solutions while the rest showed hyposensitivity; and 58 per cent showed normal reactions to olfactory sensitivity, 8 per cent had increased reactions, and 34 per cent were hypersensitive.—L. de Mello

Study of the Lysozyme Activity of Bilateral Bronchial Secretions in Patients with Pulmonary Tuberculosis (in Italian). A. Di Stefano*, T. Rossi, and E. Volpe. *Ann Med Sondalo*, No. 2, 1960, 8: 98–108. (*Villaggio Sanatoriale, Sondalo, Italy)

Lysozyme is a part of the body's natural defenses. The purpose of this study was to learn if there is some difference in the content of such a substance in bronchial secretions removed by bronchoscopy from various parts of the lung. Fifty-two samples of bronchial secretions of 26 male patients with either pulmonary tuberculosis or sequelae were tested: a turbidimetric method was used for measurement of lysozyme. It was found that the values of lysozyme activity greatly varied in the lungs, without any relationship to the quantity of secretions or the form and seriousness of the disease. No significant differences were found between these values and the presence of *M. tuberculosis* in the lung, the blood sedimentation rate, the age of the patient, and the general clinical condition.
—I. Archetti

The Tuberculous Round Lesion (in German). P. Schmidt*. *Schweiz Z Tuberk*, No. 4, 1960, 17: 250–259. (*Westerwaldklinik, Waldbreitback, Germany)

This form of pulmonary tuberculosis may develop from a primary infection, an early infiltration, caseous bronchopneumonia, or from a cavity. The cause of such a transformation is unknown. Spontaneous healing is not likely; chemotherapy may be effective. When the size of a round lesion is 4 to 5 cm., resection is indicated; if it contains a cavity or the bronchial secretion is positive for acid-fast bacilli, surgical removal is urgent. In general, resectional surgery is the best treatment, especially since a tuberculoma may be mistaken for another type—sometimes malignant—the coin lesion. Of 275 patients with tuberculomas observed from 1956 to 1959, there were 70 without cavita-

tion and with sputum negative for acid-fast bacilli, 43 negative with cavity, 138 with cavitation and positive acid-fast findings, and 24 patients who did not have cavitation but had sputum positive for tubercle bacilli.—Z. Virágh

Basic Elements in the Teaching of Tuberculosis and Respiratory Diseases to Undergraduate Students (in Spanish). O. Garcia-Rosell*. *Rev Paul Tisiol*, June–December, 1960, 21: 127–134. (*U. of San Marco, Lima, Peru)

The teaching of these subjects has expanded. The field now includes respiratory diseases of a nontuberculous nature. Such teaching is indispensable in undergraduate instruction, even if only basic and schematic for the instruction needed for the development of general practitioners. The program must include a minimum of theory, and extensive experience in dispensaries and hospitals with personal study of pathology and diagnostic methods. It must include service in centers for the epidemiology, control, and prevention of tuberculosis and related diseases.—L. de Mello

The Prognosis of 43 Apparently Cured Cases of Bilateral Tuberculosis (in Portuguese). A. Rizzo*, M. Barreto, and R. Condula. *Rev Bras Tuberc*, December, 1960, 206: 49–55. (*Sanatorium O. Freitas, Recife, Brazil)

A follow-up study was made of 86 patients who had been discharged from 1948 to 1957. Upon admission, 37 per cent had shown advanced bilateral lesions. Only 43 expatients were located. The time elapsed between discharge and review of these patients varied from a maximum of 9 years to a minimum of 3 years; 35 were alive and felt well, 5 had relapses, and 3 had died. Attention is called to the high percentage that felt well despite the gravity of their lesions. In the majority of these expatients, recuperation was attained by means that today are forgotten. The opinion is expressed that social conditions must first be changed before we may abandon the old surgical therapy of tuberculosis.—L. de Mello

The Prognosis of Open Pulmonary Tuberculosis (in German). A. Wernli-Hässig*. *Schweiz Z Tuberk*, No. 4, 1960, 17: 229–249. (*Stockerstrasse 50, Zürich, Switzerland)

Of 100 patients with open tuberculosis treated between 1936 and 1940, the disease was fatal in 44, remained stationary in 12, and became inactive in 44 cases. In a comparable group of 100 patients treated during 6 years (1948–1954) of the antimicrobial era, 6 patients died, 12 had active disease, and the disease of 82 became inactive. Of this second group, reactivation occurred in 35 patients but it was reversed by treatment in every instance. —Z. Virágh

Development of Pulmonary Tuberculosis among Workers in Tuberculosis Sanatoriums: Infection with Primarily Drug-resistant Tubercle Bacilli (in Japanese). T. Iwazaki*. *Jap J Chest Dis*, December, 1960, 19: 832–838. (*Kekkaku Yobokai Institute, Kiyose, Japan)

Between 1955 and 1960, the author made an inquiry into the development of pulmonary tuberculosis among workers in 107 tuberculosis sanatoriums which had more than 300 beds. The incidence declined from 0.80 per cent in 1955 to 0.37 per cent in 1959. A drug-resistance test was performed on 54 of 83 patients with sputum positive for tubercle bacilli. Fourteen patients were found to be victims of primarily resistant tubercle bacilli (completely resistant to 10 γ of streptomycin per ml. and 1 γ each of isoniazid and PAS per ml.). Nine strains were resistant to only 1 drug, 9 were resistant to streptomycin and PAS, and 2 strains were resistant to all 3 drugs. There were 2 physicians, 9 nurses, and 3 hospital workers. The time of primary infection occurred between the ages of 20 and 29 years in 6 patients, 30 and 39 years in 3 patients, and 40 and 49 years in 3 patients. It occurred before 1945 in 4 patients, after 1952 in 3, and at an unknown time in 7 patients. It was, therefore, not known whether some of these patients were first infected by drug-susceptible bacilli, as demonstrated by a positive tuberculin reaction, and then were later reinfected by drug-resistant bacilli, thus developing pulmonary tuberculosis which resulted in the expectoration of drug-resistant bacilli in the sputum. The incidence of development of new cases of tuberculosis in these institutions was not remarkably higher than in other public or private institutions in which careful programs of case detection were in force.—I. Tateno

Pulmonary Tuberculosis in a Hong Kong Sanatorium for Refugees. J. N. Burgess*. *Med J Aust*, December 3, 1960, 2: 910–911. (*Haven of Hope Tuberc. Sanatorium, Hong Kong)

Hong Kong's population of 3 million includes 1 million refugees from the mainland of China; 400,000 have been provided with housing from the government. Rennies Mill Camp on Junk Bay has 10,000 refugees under the jurisdiction of Taiwan. It has a general medical clinic, a maternity home, and a tuberculosis clinic. There are 60,000 cases of tuberculosis in the colony, with a death rate of 77 cases per 100,000. Outpatient clinics treat 6,000 patients, and there are 1,500 inpatient beds. There are various treatment programs, depending on the nature of the disease. Most of the disease in children is manifested by mediastinal adenopathy with little pulmonary spread. About 70 per cent of the

newborns receive BCG in the first month of life. The number of tuberculin reactors rises from 77 per cent at 14 years to 90 per cent at 20 years. There is a large backlog of patients awaiting surgical treatment because of the inadequate facilities available.—H. J. Simon

Giant Pulmonary Tuberculoma Successfully Treated with Chemotherapy (in Japanese). S. Kumagaya* and T. Ishida. *Jap J Chest Dis*, November, 1960, 19: 768–771. (*National Shonai Sanatorium, Akita Prefecture, Japan)

The writers did not believe the size of the pulmonary tuberculoma to be the only criterion to be considered in determining whether chemotherapy for a patient should be stopped and surgery instituted. They treated a 27-year-old male patient with a giant pulmonary tuberculoma (5.5 × 3.4 cm.) with chemotherapy (streptomycin, PAS, and isoniazid initially, followed by PAS and isoniazid) for 23 months. Sputum was initially negative by both microscopy and culture, but it became positive for tubercle bacilli on microscopy after chemotherapy was initiated. The tuberculoma first became smaller, then a cavitary shadow developed, and the tuberculoma finally disappeared completely. Detailed roentgenographic analysis (presence or absence of hilar lymphadenopathy, pleural adhesion, and other pathologic foci, locus of the tuberculoma, et cetera) and clinical study are considered to be important before a patient with a large tuberculoma is considered for possible surgical treatment.—I. Tateno

TUBERCULOSIS, NONPULMONARY

Mediastinal and Spontaneous Subcutaneous Emphysema in a Case of Miliary Tuberculosis (in French). Ph. Seringe* and J. L. Amiel. *Sem Hop Paris*, December 24, 1960, 106: 601–608. (*Hosp. Trousseau, Paris, France)

In a case of miliary tuberculosis in a young girl the treatment, which did not include cortisone, was interrupted too soon and the child had a relapse. Treatment was resumed, and on the seventeenth day the child developed marked dyspnea. The roentgenogram revealed mediastinal emphysema. Subcutaneous emphysema was also present. The patient recovered completely. Various possible explanations for this condition are given, but the cause could not be demonstrated conclusively. —E. Lyon

Pulmonary Endometriosis (in German). H. Sturzenegger*. *Schweiz Z Tuberk*, No. 4, 1960, 17: 259–266. (*Thunstrasse 78, Bern, Switzerland)

The case history is presented of a 52-year-old woman whose roentgenograms revealed a 4-cm. coin lesion in the right lower lung field. She had undergone a total hysterectomy with removal of the adnexa 6 years prior to admission. A wedge resection was performed. The histologic diagnosis of the tumor-like specimen removed was pulmonary endometriosis with cyst and polyp formations. This rare disorder is benign; it may develop by local metaplasia but will most likely develop as an hematogenic metastasis.—Z. Virágh

Tuberculosis of the Larynx Today (in German). H. Sighart*. *Wien Med Wschr*, October, 1960, 110: 829–830. (*Sanatoriumstrasse 2, Vienna, Austria)

Of 44 patients with tuberculosis of the larynx, 21 had not been treated previously and had far advanced phthisis; the laryngeal involvement was only a complication. The patients reacted to antimicrobial therapy with almost complete *restitutio ad integrum* in a relatively short time. The prognosis was doubtful in another group of 23 patients with inadequately treated pulmonary tuberculosis of long standing. Laryngeal tuberculosis requires adequate treatment with antimicrobials.
—Z. Virágh

Tuberculous Meningitis in Children: A Review of 167 Untreated and 74 Treated Patients with Special Reference to Early Diagnosis. E. M. Lincoln*, S. V. R. Sordillo, and P. A. Davies. *J Pediat*, December, 1960, 57: 807–823. (*N. Y. U.—Bellevue Med. Center, N. Y.)

In 241 patients with tuberculous meningitis, the dominant early symptoms were fever, vomiting, and apathy. In the 74 treated cases, the survival rate could be directly correlated with the stage of the disease at onset of therapy. Tuberculosis should always be suspected as the cause of fever and other general symptoms which begin during convalescence from measles. Symptoms of upper respiratory infection frequently obscured early tuberculous meningitis. A history of contact, a positive tuberculin reaction, and roentgenographic evidence of pulmonary tuberculosis were important factors in diagnosis. In the differential diagnosis of children with signs of neurologic origin, a chest roentgenogram should be obtained. A tentative diagnosis can be made in practically every case by examination of the cerebrospinal fluid. Treatment should not await bacteriologic confirmation. Serial lumbar punctures should be performed to evaluate the course of the disease. In survivors, an ultimate prognosis can be estimated only after prolonged observation and evaluation of electroencephalographic and psychometric studies (after authors' summary).—M. J. Small

Short-Term Antimicrobial Therapy of Tuberculous Meningitis. E. L. KENDIG* and C. D. BURCH. *Amer J Dis Child,* November, 1960, 100: 696. (*Medical College of Virginia, Richmond)

Due to various economic factors, poor housing arrangements, and failure in projected follow-up, 19 children surviving tuberculous meningitis received a course of antimicrobial therapy, including isoniazid, streptomycin, and PAS for periods of 12 months or less. The results were considered good in 14. In 11 of the 19 surviving patients, antimicrobial therapy was carried out over periods of 8 months or less, and the results were considered good in 8. Three of the survivors had associated miliary tuberculosis. It is suggested that many cases of tuberculous meningitis may be effectively managed by a 12-month course of antimicrobial therapy, including isoniazid.—M. J. SMALL

Effect of Treatment on Ophthalmic Lesions Caused by Tuberculous Meningitis (in Finnish). P. MIETTINEN* and O. WASZ-HÖCKERT. *Duodecim,* October, 1960, 76: 839–843. (*Lastenklinikka, Helsinki, Finland)

Eye symptoms were present in 65 per cent of 193 patients with tuberculous meningitis treated in Children's Hospital from 1949 through 1954. During these years the treatment progressed from streptomycin alone to the employment of streptomycin, PAS, isoniazid, and cortisones in a group of 37 patients.

No differences were observed in the various treatment groups regarding the disappearance of muscular pareses of the eye. Papilledema improved more rapidly as the treatment developed. The greatest difference was seen in the cicatrization of the choroidal foci. In this respect, the average recovery period was shortened from 6 to 2 months. —J. HAAPANEN

Tuberculosis of the Tongue (in Hungarian). J. BENE* and B. SZENTKERESZTI. *Tuberkulozis,* June, 1960, 6: 179–180. (*U. of Debrecen, Hungary)

The case history is presented of a 35-year-old woman with miliary tuberculosis. At least 2 small painless nodules were observed on the tongue; the biopsy specimen disclosed granulomas with numerous tubercle bacilli. The patient was cured by antimicrobial treatment.—Z. VIRÁGH

Tuberculous Uterine Synechiae (in French). R. SOLAL*, J. BOUCHARA, and M. LEGROS. *Presse Med,* December 10, 1960, 55: 2126–2129. (*Oran, Algeria)

Netter and Musset have defined a new clinical entity called Netter and Musset's disease. The disease occurs frequently in Moslem women in North Africa. The predominant feature is amenorrhea and the picture of uterine symphysis as shown on hysterogram. The origin of this disease proved in many cases to be tuberculous, as demonstrated by cervical biopsy and guinea pig inoculation or culture of the cervical secretion. It is assumed that this condition is caused by tuberculous lesions in the endometrium with tissue destruction. The treatment is routine antituberculous drug therapy. In exceptional cases surgical intervention may be indicated. Two patients are reported who were successfully operated on and in whom normal functions of the endometrium were restored. —E. LYON

UPPER RESPIRATORY TRACT DISEASE, VIRAL

Susceptibility and Immunity to Common Upper Respiratory Viral Infections—The Common Cold. G. JACKSON*, H. DOWLING, T. ANDERSON, L. RIFF, J. SAPORTA, and M. TURCK. *Ann Intern Med,* October, 1960, 53: 719–736. (*U. of Illinois, Chicago)

Studies in volunteers have shown that the common cold syndrome can be produced by uncharacterized filtrable agents in the nasal secretions of persons with common colds. The experimental illness resembled that resulting from natural infection. The predominant features were afebrile coryza with increased nasal discharge and congestion, but different viruses produced a greater or lesser degree of noncoryzal pharyngitis, and occasionally a febrile respiratory infection. Subclinical infections were shown by observing the cytopathogenic effect of infection on the cells of the nasal mucosa. Common cold viruses were demonstrated in the nasal epithelial cells and in the cell-free nasal secretion. The secretions from symptomatic donors usually contained more than 100 infectious doses per milliliter. Certain persons who reported proneness to natural infections frequently developed coldlike symptoms from the instillation of noninfectious salt solution, but they showed no greater susceptibility to infectious material than did other volunteers. A small group of persons were resistant to natural and experimental infections. Although psychologic factors were important in some respects, prediction of susceptibility from psychologic studies was not successful. Under experimental conditions, neither total body chilling nor frigid conditions induced spontaneous infections or increased susceptibility to experimental infection. Sleep deprivation and fatigue increased infectivity insignificantly. Girls showed significant differences in susceptibility in relation to different phases of the menstrual cycle. Pooled human

gamma globulin neutralized the infectivity of several viruses associated with natural common colds. Immunity to specific common cold viruses was shown by rechallenging volunteers with the same and with different infectious nasal secretions. It is suggested that the common cold syndrome in man is caused by specific viral infections, each of which elicits an appropriate immune response (after authors' summary).—T. H. NOEHREN

Infections Due to Coxsackie Virus Group A, Type 9, in Boston, 1959, with Special Reference to Exanthems and Pneumonia. A. M. LERNER*, J. O. KLEIN, H. S. LEVIN, and M. FINLAND. *New Engl J Med*, December 22, 1960, 263: 1265–1272. (*Harvard Med. School, Boston, Mass.)

Fifteen cases are described of infection due to Coxsackie virus Group A, Type 9, observed at the Boston City Hospital in 1959. Aseptic meningitis and maculopapular, petechial, or vesicular rashes, as well as pneumonia, were associated with these infections. Isolation and neutralization tests in tissue culture strongly related Coxsackie virus Group A, Type 9, with these illnesses. Virus was isolated from the throat, rectum, and cerebrospinal fluid, as well as from the blood of patients who recovered. The clinical, pathologic, and virologic findings in a 16-month-old patient with pneumonia and central nervous system complications are presented. The virus was recovered from the lung and liver in titers that indicated replication in those organs (after authors' summary).
—M. J. SMALL

Acute Respiratory Disease Caused by ECHO Virus. Report of an Epidemic in a Nursery (in Japanese). K. NAKAMURA*, T. KITAYAMA, H. HUKUMI, H. NISHIKAWA, and Y. HARA. *Diagnosis & Treatment*, December, 1960, 48: 1975–1981. (*Kanto Teishin Hosp., Tokyo, Japan)

An epidemic of acute respiratory disease is described which occurred in a nursery in September, 1959, in which 22 of 24 (92 per cent) of the babies in the institution were affected. The main clinical features of the disease in most patients were fever and signs of acute upper respiratory tract infection. In addition, low-grade toxemia, lymphadenopathy, and rubella-like exanthems were each present in 3 patients, diarrhea occurred in 14 (3 with bloody stools), and vomiting occurred in 9 patients. ECHO virus type 1 was isolated from 2 of 11 throat swab samples by HeLa cell culture, and in 4 of 8 fecal specimens by monkey kidney cell culture. A fourfold or greater increase in neutralizing antibody titer was demonstrated in 10 of 12 paired serum samples. Adenovirus type 2 was isolated in 2 of 11 throat swab samples by HeLa cell culture, but none of the 11 paired serum samples tested showed an increased neutralizing antibody titer. It is concluded that this epidemic was caused by an infection with the ECHO virus type 1.—I. TATENO

THORACIC SURGERY

Bronchial Carcinoma: Lobar Distribution of Lesions in 250 Cases. L. GARLAND*. *Calif Med*, January, 1961, 94: 7–8. (*U. of California School of Med., San Francisco)

Following a study of the lobar distribution of lobar pneumonia in young persons, it was decided to examine the distribution of proved primary bronchial carcinoma in the same institution; 250 consecutive cases were analyzed up to May, 1960, with autopsy records being available in approximately ⅓ of the cases. The sex ratio was 5 males to 1 female, ages ranged from 35 to 85, and ⅔ of the patients were whites. There was apparently no correlation of the lobar site of these tumors with the lobar location of childhood pneumonic lesions. Slightly more than 50 per cent of the tumors originated in the upper lobes; 133 were on the right as against 112 on the left side, plus 3 involving the carina in both upper lobes equally.
—E. A. ROUFF

Primary Chondrosarcoma of the Lung. E. A. SMITH*, R. V. COHEN, and A. R. PEALE. *Ann Intern Med*, October, 1960, 53: 838–846. (*USAF Hosp., Larson AFB, Washington, D.C.)

Chondrosarcoma is a relatively uncommon tumor, and is exceedingly rare in the lung. A case is presented of primary chondrosarcoma of the lung of at least 11 years' duration. Extensive search for a primary site of the lung lesion, which was proved by open chest biopsy, failed to reveal an extrapulmonary source. The lesion was considered to be definitely malignant on the basis of the histopathologic features.—T. H. NOEHREN

Primary Hemangiopericytoma of the Lung Successfully Treated by Surgery (in Japanese). K. KAIDA*, K. TANAKA, and N. SHINKAI. *Jap J Chest Dis*, January, 1961, 20: 39–42. (*Tuberculosis Institute of Kyushu U., Hukuoka, Japan)

A case is reported of primary hemangiopericytoma of the lung seen in a 37-year-old male patient. He had a coin lesion in the left mid-lung field and received treatment for pulmonary tuberculosis for a year, but the pulmonary lesion increased in size and he was sent to the hospital. He underwent left upper lobectomy with a suspected diagnosis of lung cancer, but the histology

of the resected specimen turned out to be typical of hemangiopericytoma as reported by Stout (1949). The patient had no recurrence of the illness 4 years after surgery. The Japanese literature was reviewed and only several reports of hemangiopericytoma were found, but none primarily in the lung.—I. Tateno

Spontaneous Idiopathic Hemothorax (in French). D. Vassiliou* and P. Lazarou. *Presse Med*, November 23, 1960, 52: 1998–2001. (*Hosp. "La Reine Frederique," Athens, Greece)

An idiopathic pneumothorax developed in a 28-year-old workman who had no history of pulmonary disease. The onset was manifested by sudden pain and paleness of the face. The chest roentgenogram gave the picture of a pleural effusion. The diagnosis of hemothorax was made when blood was aspirated. Further investigation failed to reveal a pneumothorax or any pulmonary or pleural lesions. The blood was removed, a pneumothorax was instituted, and blood transfusions, antimicrobials, and supportive medicines were given. The patient made a satisfactory recovery. Very few cases of this type are known in the literature.—E. Lyon

Lobectomy for Metastatic Leiomyosarcoma of the Uterus. C. G. McEachern, M. M. Gitlin, and R. E. Sullivan. *JAMA*, November 26, 1960, 174: 1734–1735.

Right lower lobe resection was performed for an asymptomatic coin lesion in a 53-year-old woman who had undergone an hysterectomy for leiomyosarcoma 2 years previously. The pulmonary lesion proved to be a metastatic leiomyosarcoma. The patient was well and free from recurrence 40 months later.—H. Abeles

Postoperative Massive Collapse of the Lung. J. G. Raffensperger, W. G. Diffenbaugh, and E. L. Strohl. *JAMA*, November 12, 1960, 174: 1386–1388.

Two patients who were surgically treated for esophageal obstruction died of severe pulmonary collapse immediately after the operation. Postmortem examinations failed to reveal the usual causes of atelectasis. The prolonged anesthesia with depressing drugs, the rapid absorption of highly diffusible gases at the termination of anesthesia, and reflex bronchospasm are considered the causes of this syndrome. To prevent this complication, the use of repeated doses of atropine, hyperventilation with room air at the end of anesthesia, and mechanical respiratory assistance in selected cases are suggested.—H. Abeles

Pulmonary Infections in Children with a Partial Thoracic Stomach ("Hiatus Hernia"). I. J. Carré*. *Arch Dis Child*, October, 1960, 35: 481–483. (*U. of Belfast, Ireland)

The occurrence of pulmonary infections in 78 children with hiatal hernias has been related to the specific symptoms referable to the patients' gastroesophageal abnormality. It was found that the incidence of pulmonary infections was considerably increased if night vomiting was a symptom. It is suggested that the cause for this is an inhalation of vomited material during sleep.—J. Lorber

The Fate of the Partial Thoracic Stomach ("Hiatus Hernia") in Children. I. J. Carré* and R. Astley. *Arch Dis Child*, October, 1960, 35: 484–486. (*U. of Belfast, Ireland)

In a retrospective study of 147 patients with the probable diagnosis of partial thoracic stomach, 117 were examined some 10 to 18 years later: 52 subjects had typical histories and, of these, 35 still showed evidence of partial thoracic stomach at roentgenographic examination; of 65 less typical cases, only 4 had positive roentgenographic evidence. In spite of the typical history and the roentgenographic evidence of partial thoracic stomach, the large majority were symptom-free. Since 1951, most children with proved thoracic stomach had been operated on. The few who did not have surgery still had roentgenographic evidence of the condition years later. These patients did not have any medical treatment. Finally, 20 patients with proved cases had been adequately treated by sustained postural treatment before they were 3 months of age. They were kept in a sitting position throughout 24 hours for at least 6 months. Although they became symptom-free, the incidence of roentgenographically demonstrable lesions remained high after 5 years of observation. Postural treatment did not increase the chances of roentgenographic cure.—J. Lorber

Patent Ductus Arteriosus in Infancy. O. Scott* and G. F. Gearty. *Arch Dis Child*, October, 1960, 35: 465–474. (*Royal Liverpool Children's Hosp., England)

A consecutive series of 28 infants whose sole cardiac anomaly was a persistent patent ductus arteriosus is reviewed. In early infancy, the typical physical signs are often missing, but a high pulse pressure is constant and is a most valuable sign. Most infants, nevertheless, also had a continuous murmur, unless there was marked pulmonary hypertension. Phonocardiography is a valuable aid to diagnosis. Roentgenographic changes are common although not diagnostic, and the electrocar-

diogram (ECG) may be normal even in severe cases. In most, however, the ECG is abnormal, and isolated left ventricular hypertrophy is the commonest finding. Cardiac catheterization is only necessary if the diagnosis is in doubt, which is unusual. Surgical treatment is essential and is best done as soon as the diagnosis is made so long as there is no heart failure or infection. Of the 28 infants, 24 had been operated on; there were no deaths.—J. LORBER

Does a Carcinomatous Scalene Node Contraindicate Pulmonary Resection? L. PINKERS* and G. LAWRENCE. *Dis Chest*, November, 1960, 516–518. (*Mason Clinic, Seattle, Washington)

Scalene node biopsy is of proved value in the diagnosis of pulmonary malignancy, and also has prognostic significance. The mean life expectancy in 24 patients with malignancy proved by biopsy was 3.6 months, the majority surviving 3 months or less, and the longest survival time being 15 months. Those who survived longest had undifferentiated carcinoma treated with irradiation. The infrequency of pulmonary complications (pneumonitis, abscess, or significant hemoptyses) cannot justify resection in these cases.—E. A. ROUFF

Ivalon Sponge Prosthesis with Pulmonary Resections Over Five Years' Experience. J. DAILEY* and J. SEAMAN. *Dis Chest*, December, 1960, 37: 604–615. (*Houston, Texas)

The ideal substance to fill body cavities and maintain collapse of the lung has long been sought. This report presents data on 111 cases of partial or total resection of the lung in which the Ivalon sponge has been used as a *prosthesis* to fill the space created by the resection. Of the total of 111 patients, 87 are living. Of the living, 22 have had the sponges in place more than 5 years, 12 for more than 4 years, 14 for more than 3 years, 9 for more than 2 years, and 30 for more than 1 year. To date, 10 per cent have become infected. Seventy-six of the operations were performed on tuberculous patients, 71 of whom are still alive; 31 were for cancer of the lung, and 12 are still alive. Four of the 24 deaths occurred during the postoperative period.—E. A. ROUFF

Resectional Therapy for Pulmonary Tuberculosis at Sunmount, 1950–1957, 807 Cases. IV. Pulmonary Resection for Tuberculosis without Effective Chemotherapy. V. KIMEL*. *Dis Chest*, November, 1960, 38: 507–515. (*Sunmount Veterans Hosp., New York)

The importance of effective chemotherapy before and after resectional therapy for tuberculosis is emphasized by the poor surgical results obtained in the reported group of patients as compared with patients from the same institution who had effective chemotherapy. Major complications, frequent relapses, and failure to achieve noninfectious sputum were forbiddingly high in the open-positive cases. The high relapse rate in the open-negative group emphasizes the need for an adequate period of effective postresectional chemotherapy.
—E. A. ROUFF

One Hundred and Forty-Eight Resections for Cavitary Tuberculosis. Correlation between Bacterial Resistance and Coverage of Operation with Chemotherapy (Isoniazid, Ethionamide, Streptomycin, Cycloserine) and the Development of Homolateral Tuberculous Complications (in French). L. MARION*, J. MARCHESE, and J. AIGUEPERSE. *Rev Tubere (Par)*, September–October, 1960, 24: 998–1024. (*Villiers-sur-Marne, France)

The results in 140 patients with cavitary tuberculosis and positive sputum who were surgically treated between January, 1955, and July, 1959, were studied. The over-all incidence of complications was 22 per cent. Of the 42 pneumonectomies, there were 5 deaths (1 hemorrhage, 4 empyemas), and 7 patients developed severe complications (empyema, progression of tuberculosis). The 36 cases of segmental resection had the highest incidence of complications (36 per cent); most of these involved empyema. There was a correlation between incidence of complications and coverage with antituberculous drugs. The incidence of complications was 11 per cent if patients were susceptible to 2 drugs, 16 per cent if there was susceptibility to 1 drug, and 42 per cent if the patients were resistant to all available drugs. Only 10 per cent of the patients were susceptible to isoniazid at the time of operation. No complications developed in this group. Ethionamide appeared to be the best preoperative drug in cases of isoniazid resistance.—V. LEITES

Thoracoplasty in the Treatment of Pulmonary Tuberculosis (in Italian). W. FROEHLICH*. *Schweiz Z Tuberk*, No. 5, 1960, 17: 328–330. (*Sanatorio Cantonale, Piotta, Switzerland)

Thoracoplasty can be employed in the treatment of postpleuritic tuberculosis and to complement other collapse therapy measures without invading the territory of resectional surgery.
—Z. VIRÁGH

Experience with Resection in the Treatment of Pulmonary Tuberculosis (in Portuguese). B. J. F. DE ALMEIDA*, L. LOSSO, R. DE ALMEIDA, and B. J. ZERBINI. *Rev Paul Tisiol*, March–June,

1960, 21: 101–112. (*Hosp. Sao Luiz Gonzaga, Jacana, Sao Paulo, Brazil)

A presentation is made of an evaluation of 566 resections in 563 patients during the period from February, 1949, to December, 1958. The indications for operative intervention were divided into 2 groups: (*1*) obligatory intervention, including unilateral tuberculosis (102 cases); tuberculomas, atelectases, fibrosis, bronchiectasis, and large cavities of the upper lobe with bronchial tuberculosis (91 cases); and failure of collapse therapy (75 cases); (*2*) selective intervention in those cases in which resection was indicated in preference to collapse therapy. Some patients did not receive preoperative antimicrobial therapy as they were operated on in 1946; others received only streptomycin as preoperative therapy or were submitted to treatment with multiple antimicrobials. Keeping in mind the above indications for operative intervention, the patients were divided into 4 groups for evaluation of the results and complications. The last of these 4 groups contained the cases with the best results, 308 cases. In this group there were 89.2 per cent clinical cures, bronchial fistulas occurred in 9.7 per cent, and the total mortality was 2.9 per cent. In this group (308 cases) of selected patients pneumonectomy was responsible for clinical remissions in 92.8 per cent of the patients, with a mortality of 5.7 per cent; lobectomy resulted in 90 per cent clinical cures, with a mortality of 2.5 per cent; and combined lobectomy and segmentectomy resulted in 75.6 per cent clinical cures, with no mortality.—L. DE MELLO

ROENTGENOGRAPHY

Congenital Adenomatoid Malformation of Lung with Pneumothorax. R. G. SPECTOR*, A. E. CLAIREAUX, and E. R. WILLIAMS. *Arch Dis Child*, October, 1960, 35: 475–480. (*Queen Charlotte Hosp., London, England)

A premature stillborn infant was found to have postmortem roentgenographic evidence of a right-sided pneumothorax with a complex loculated appearance. Necropsy confirmed a right pneumothorax due to a ruptured cystic hamartoma of the lung which occupied the right upper lobe. The remaining lung tissue was hypoplastic. A full discussion follows to define the relationship between congenital cystic disease of the lung and true hamartoma.—J. LORBER

Development of Atelectasis following Bronchography (in Japanese). T. OGURA* and Y. INAGAKI. *Clin Resp Organs*, December, 1960, 15: 861–864. (*Nihon Med. College, Tokyo, Japan)

Two cases of atelectasis following bronchography are reported. Both occurred in patients with pulmonary tuberculosis, a 23-year-old female and a 58-year-old male. The atelectasis developed on the left side in the female and on the right side in the male; both cases occurred on the side into which the radiopaque material was injected. The atelectases were benign and disappeared within 3 days in both patients. They developed neither fever, cough, chest pain, nor bloody sputum, and no recurrence of atelectasis was observed. The writers conclude that this type of complication was the first they had experienced, although they had made about 1,000 bronchographic examinations. The pathogenesis of atelectasis is discussed, and various direct and indirect causes, including bronchospasm and bronchial obstruction, are mentioned.—I. TATENO

Noninfectious Necrotizing Granulomatosis: The Pulmonary Roentgen Signs. M. E. BISCHOFF*. *Radiology*, November, 1960, 75: 752–756. (*St. Luke's Hosp., Denver, Colo.)

Four cases are presented of noninfectious necrotizing granulomatosis (a term embracing such entities as Wegener's granulomatosis, Churg and Strauss' granulomatosis, midline lethal granuloma, allergic or hypersensitivity angiitis, and pulmonary granulomatosis). Roentgenographic changes, when present, may represent a myriad of pathologic processes. Nonspecific changes are due to bronchopneumonia, congestion and edema, and pulmonary infarction. The specific changes are caused by the granulomas and the necrosing lesions in the vessels. These are seen as single or multiple nodules and infiltrates which are chronic, and which may or may not have central cavitation. They are most likely to be confused with alterations arising from metastatic neoplasm, infectious granulomatosis, or a fibrosing process. It is important to evaluate the roentgenographic signs in the light of clinical manifestations. This disease will be diagnosed more readily if the roentgenographic interpretation is augmented by an evaluation for evidence of an allergic history, facial lesions, respiratory tract disease, renal disease, skin changes, and eosinophilia.—W. J. STEININGER

An Investigation in Volunteers Undergoing Mass-Radiography Examination in the City of Canterbury, 1958. J. S. JONES*. *Tubercle*, December, 1960, 41: 441–447. (*Royal Sea Bathing Hosp., Margate, England)

It is recognized that some patients referred for investigation from mass roentgenography units have symptoms. Although this observation has

occasionally been confirmed, the implication that on a national scale large numbers of sick people may be attending such units has not been entertained. Since tuberculosis is the only disease which can reasonably be excluded on the basis of a chest roentgenogram, it will be increasingly important to consider the problem of mass roentgenography volunteers with symptoms caused by other diseases if the tuberculosis yield from mass filming units continues to fall during the next few years. Questioning of 922 volunteers at a mobile mass roentgenography unit in the city of Canterbury in 1958 showed that 10.4 per cent of the people came because of symptoms of respiratory disease, and 6.4 per cent came because of a history of contact with tuberculosis. A history of respiratory disease, the presence of nonrespiratory symptoms, and a desire for company were among other reasons given for attending. The evolution of so-called mass roentgenography is already guiding it toward the examination of the sick ("G.P. referrals" and static units), and it seems that some form of clinical mediation may eventually be necessary in all branches of this work if the individual, as well as the community, is to get the best value from this important method of investigation.
—M. J. SMALL

Roentgenographic Classification of So-called Radiation Fibrosis of the Lung (in Japanese). H. OKA*. *Clin Radiol (Tokyo)*, January, 1961, 6: 15–29. (*Kekkaku Yobokai Institute, Kiyose, Japan)

The morphologic characteristics are described of radiation fibrosis of the lung seen in 52 patients with breast cancer who had received deep radiation therapy following surgical treatment and who had no metastases in the lung field. They were detected roentgenographically from 95 cases so treated. As all of the films showed the same character of opacities, the roentgenographic findings were divided into 5 categories on the basis of the size and extent of the shadow. They were termed acinar, lobular, segmental, lobar, and strangular opacities. The term "fibroatelectasis" was coined to describe the roentgenographic shadow of the radiation injury based on the morphologic characteristics of the lesion. Criteria are described which should be used in classifying fibroatelectasis of the lung into the various types; representative examples are presented.—I. TATENO

Some Biomedical Problems of the Nuclear Age. C. L. DUNHAM*. *Radiology*, November, 1960, 75: 815–819. (*U. S. Atomic Energy Commission, Washington, D.C.)

Health problems associated with the nuclear age fall into 3 principal categories. The first concerns the definition of the dose and dose-rate relationships which exist between radiation exposure and biologic effects. The second concerns the relationship between the concentration of a given radio-element in the environment (air, food, and water) and the resultant exposure to any given organ of the body. The third concerns the development of effective prophylaxis and treatment of whole-body and local radiation injury. Experimental facts strongly suggest that formation of a single ion pair is the unitary event which leads to the induction of a mutation and, hence, that all radiation absorbed in genetic material, regardless of dose or dose rate, is fundamentally mutagenic. Recent work with continuous exposures at dose rates from a few tens of r down to one r or less per week, however, suggests that there indeed may be, from a practical standpoint, a threshold for some of the deleterious effects of radiation (such as curtailment of life span, leukemia, or tumor induction), or that, at worst, the effects are very greatly reduced. Unsolved problems pose a challenge to the ingenuity and patience of the radiation biologist, the radiologic physicist, and the molecular biophysicist.—W. J. STEININGER

CHEMOTHERAPY

Changing Concepts in the Treatment of Tuberculosis. Part I. W. G. TELLESSON*. *Med J Aust*, December 24, 1960, 2: 1005–1007. (*Sydney Hosp., Australia)

Three major fallacies have become widely current in both the lay world and the medical profession concerning the present position of antituberculosis treatment. First, there is the impression that tuberculosis has been eradicated. The facts are that mortality has declined sharply and morbidity has fallen somewhat, but tuberculosis still remains the most important infectious disease. Other infectious diseases seasonally displace it with respect to frequency of notification, but tuberculosis steadfastly remains near the top of the list of notifiable diseases. Second, it is believed that most new patients are found at an early stage of their disease. Actually, the proportion of patients found to have moderately or far advanced disease has not fallen. Moreover, there has been a slight rise in the proportion of cases for which the first notice is the death certificate. Third, tuberculosis is considered a disease of old age. In actual fact, in males the peak incidence of notification falls between 45 and 50 years of age, and in females, between 30 and 35 years of age. The para-

dox lies in the fact that, with more effective therapy available, there are more cases of tuberculosis. The explanation would seem to rest in part on the fact that therapy prevents mortality and lowers the death rate, so that a greater fraction of the population lives with a present or past history of tuberculosis. Elderly patients in whom tuberculosis was arrested by chemotherapy also form a reservoir for later reactivation. Chemotherapy also poses a new problem. The uncooperative patient may expose the community to infection by drug-resistant organisms. Contacts of such patients may develop infections against which the modern armamentarium offers little aid. In the past, the uncooperative patient shared the same over-all expectation of life; now most remain a hazard to their fellows for years. Diagnostic procedures remain essentially the same as they have been for many years. However, an apparent lack of physician and patient awareness of the possibility of tuberculosis is stressed. It is emphasized that the most neglected field in the therapy of the patient with tuberculosis lies in the area of rehabilitation, and a strong plea is raised for physician–patient–prospective employer cooperation as well as a better public relations attitude for prospective co-workers of rehabilitated ex-tuberculosis patients.—H. J. Simon

Changing Concepts in the Treatment of Tuberculosis. Part II. T. Selby*. *Med J Aust*, December 24, 1960, 2: 1007–1010. (*Pulmonary Clinic, Sydney, Australia)

An historical approach to the general care, chemotherapy, and surgical management of the tuberculous patient is presented with a commentary on the changing concepts regarding each form of therapy. Present concepts seem to run along the following lines: Early hospitalization is advised for the institution of drug therapy and susceptibility tests, but domiciliary treatment is not considered detrimental. On the whole, most drug regimens include 2 chemotherapeutic agents (isoniazid and PAS or streptomycin). The period of bed rest and isolation is becoming shorter, and most physicians favor early ambulation and return to work. The duration of chemotherapy has at least doubled, and a minimum of 2 years is considered essential. Indefinite continuation of therapy has recently emerged as a point of consideration and controversy. Surgical intervention is used less frequently and more selectively, and is usually instituted when medical therapy has failed. Corticosteroids in conjunction with effective chemotherapy are reserved for acutely ill patients and for disease involving the serous membranes.
—H. J. Simon

Treatment of Pulmonary Tuberculosis with Antimicrobials and Corticosteroids (in German). H. Steinlin*. *Schweiz Z Tuberk*, No. 5, 1960, 17: 363–370. (*Oberer Graben 11, St. Gallen, Switzerland)

During a 6-week period of treatment with corticosteroids, PAS, isoniazid, and streptomycin, the sputum of 23 of 26 patients became negative for acid-fast bacilli, and 18 of 23 cavities disappeared or considerably decreased in size. The improvement was most marked in exudative processes.
—Z. Virágh

The Tuberculous Cavity and Corticosteroids (in German). K.-B. Lee*. *Beitr Klin Tuberk*, August, 1960, 122: 333–356. (*Teaching Hosp., Taegu, Korea)

In addition to the isoniazid–streptomycin regimen, corticosteroids were administered to 89 patients with cavitary pulmonary tuberculosis. The antimicrobial treatment continued for several months; corticosteroids were given for an average of 2 months. All of the cavities did not respond uniformly to the treatment. The best result was recorded in untreated solitary cavities. Susceptibility of the infecting organism to isoniazid is a *conditio sine qua non* in administering corticosteroids to tuberculous patients.—Z. Virágh

Cortisone and Tuberculosis (in Portuguese). N. Bethlem*. *Rev Bras Med*, September, 1960, 17: 826–837. (*Consultant to the journal)

Three time periods in the development of the use of cortisone in tuberculosis are discussed: (*1*) the hormone was believed to be contraindicated; (*2*) clinical and experimental studies showed that with isoniazid, streptomycin, and PAS the tuberculous healing was not impeded, and that cortisone could be used when indicated for some other concurrent condition; (*3*) in tuberculous meningitis and pleurisy, cortisone could be used for treatment of the intense fibrous tissue formation. Once these points were determined, cortisone became an adjunct treatment of tuberculosis along with antimicrobial drugs, especially in cases of localized serous reaction, in the final stages of the infection, and in extensive mediastinal adenopathy in infants.—L. de Mello

Remarks on the Therapeutic Activity of Ethionamide (in Italian). V. Nitti*, E. Miraglia, and R. Virgilio. *Arch Tisiol*, No. 10, 1960, 15: 971–995. (*U. of Naples, Italy)

Twenty-five male patients, 16 to 67 years of age, with various forms of pulmonary tuberculosis and with normal renal function, were given 1 gm. of ethionamide daily for a period of at least 60 days; thereafter, they were treated either with

the same substance in combination with other antimicrobials, or with different therapeutic procedures. Tolerance to ethionamide was good in 14 patients and less good in the remaining 11, 2 of whom presented serious untoward symptoms so that treatment had to be discontinued. The results are therefore based upon 23 cases. In a few patients with a more marked evolutive tendency, improvement was preceded by a short period of exacerbation of the symptoms; except in the more severe cases, there was an evident decrease, followed by disappearance of both cough and sputum and a lowering of the temperature. On roentgenographic examination, the action of the antimicrobial was found to be particularly good upon initial forms of the disease: cavities closed and fluids disappeared. Tuberculin reactions were more severe in the first week of treatment, but tended to normalize after a certain time. In early cases, the sputum became negative for tubercle bacilli. Microbial resistance developed readily, especially in markedly evolutive cases. Therefore, it should be kept in mind that the use of ethionamide alone may result in bacillary resistance.—I. Archetti

Ethionamide (1314Th) and Viomycin in the Treatment of Resistant Pulmonary Tuberculosis. J. R. Edge* and J. C. P. Weber. *Tubercle,* December, 1960, 41: 424–429. (*High Carley Hosp., Ulverston, England)

Fourteen patients with chronic tuberculosis that was fully resistant to the standard antimicrobial agents were treated with ethionamide together with viomycin, 1 gm. daily of each. In 4 the viomycin had to be stopped due to the development of nerve deafness in 3 and vestibular symptoms in 1, and pyrazinamide was given. The sputum of 5 patients rapidly became negative for tubercle bacilli on microscopy and culture (in 1 after a pneumonectomy), and in 3 this status was maintained. In 5 the sputum remained persistently positive, and in 2 cases cultures with increased resistance to ethionamide appeared; in the remaining 4 no conclusions could be drawn about the effects of the drugs. The ethionamide was reasonably well tolerated and had to be discontinued in only 1 instance.—M. J. Small

High Dosage Isoniazid in Original and Retreatment Chemotherapy for Pulmonary Tuberculosis: Clinical, Electrophoretic and Bacteriological Studies. H. Mark* and P. Thode. *Dis Chest,* January, 1961, 39: 18–27. (*V. A. Hosp., Livermore, Calif.)

The study regimen consisted of 800 mg. of isoniazid and 100 mg. of pyridoxine daily. The high dosage proved to be of little value for those patients who had not responded to previous chemotherapy; previously untreated patients did well on this high dosage. Practically no toxicity was encountered. Serum protein electrophoretic patterns were useful in following the physiologic reaction to the disease. Total protein values were always within the normal range: elevated alpha globulins appeared in the exudative processes, and high beta or gamma fractions in the fibrotic cases. —E. A. Rouff

Inactivation of Isoniazid (in French). H. Bonstein*, G. Rossi, and G. Favez. *Schweiz Z Tuberk,* No. 5, 1960, 17: 331–341. (*Clinique Sylvana Epalinges/Lausanne, Switzerland)

A single dose of 500 mg. of isoniazid was ingested by 83 patients with sputum positive for acid-fast bacilli, and the amount of free isoniazid was determined in the urine output 24 hours after ingestion. Patients who excreted less than 10 per cent of the isoniazid were considered rapid inactivators; those who eliminated more than 10 per cent were the slow inactivators. On the basis of this arbitrarily-chosen limit, there were 36 rapid and 57 slow inactivators. After 9 weeks of treatment, conversion occurred in 85 per cent of the rapid and in 70 per cent of the slow inactivators, and the size of the cavities decreased about equally in both groups.—Z. Virágh

On the Plasma Concentration of Active Isoniazid in Twins (in Japanese). S. Okinaka*, S. Yoshida, R. Mikami, and S. Kita. *Kekkaku,* January, 1961, 36: 27–31. (*Tokyo U., Japan)

The writers studied the serum concentrations of active isoniazid in 54 pairs of twins (43 monozygotic co-twins and 11 dizygotic co-twins) 11 to 14 years of age. The serum was obtained 4 hours after oral administration of 4 mg. of isoniazid per kg. of body weight. Similar plasma concentrations of isoniazid were observed more frequently in monozygotic twins than in dizygotic twins. The latter consisted of those showing similar or dissimilar serum concentrations of the compound. It was concluded that the individual variation in the mode of inactivation of isoniazid depended upon the genetic determinant. The 4-hour serum concentrations of isoniazid in 108 twins were divided into 3 groups of different ranges, i.e., the mean concentrations in the 3 groups were 0.12, 0.50, and 1.68 γ per ml., respectively, and the difference was statistically significant. The same relationship was observed in 41 tuberculous patients. The authors concluded from these observations that the first, second, and third groups might be regarded as the rapid, intermediate, and slow inactivators of isoniazid, and that these groups showed the general patterns of isoniazid metabolism in Japanese.—I. Tateno

Isoniazid and Pyridoxine (in Portuguese). I. DA SILVEIRA*. *Rev Bras Med*, June, 1960, 17: 528. (*Editorial consultant)

The peripheral neuropathy seen in patients undergoing isoniazid treatment is not a serious problem when the dosage is limited to 300 mg. per day. Nevertheless, this dosage may have to be increased in certain cases, as it is known that the drug is metabolized into derivatives that have little antimicrobial effect. Larger doses have to be used in a great number of cases. With the addition of 50 to 450 mg. of pyridoxine in combination with isoniazid it is possible to avoid the appearance of peripheral neuropathy. The exact dosage of pyridoxine is not definitely known. Everything seems to indicate that 10 mg. for each 100 mg. of isoniazid are sufficient.—L. DE MELLO

Lack of Any Antagonism Between Pyridoxine and Isoniazid in the Chemotherapy of Acutely or Chronically Tuberculous Mice. A. J. CROWLE* and D. K. RIEMENSNIDER. *Tubercle*, December, 1960, 41: 450–453. (*U. of Colorado School of Med., Denver)

Evidence is presented that pyridoxine did not diminish the antituberculous effect of isoniazid in acutely or chronically tuberculous mice whether isoniazid treatment was substantial or minimal, and regardless of which in a wide range of vitamin-to-isoniazid ratios was employed. These results, along with others from various laboratories, which are discussed, support the accumulating evidence that pyridoxine can be used along with isoniazid in the chemotherapy of tuberculosis with little fear that practical inhibition of the curative effects of isoniazid will result (after authors' summary).—M. J. SMALL

The Effect of Kanamycin on the Postoperative Course of Lobectomy in Patients with Streptomycin-resistant Tubercle Bacilli (in Japanese). THE CHEMOTHERAPY OF TUBERCULOSIS UNIT OF THE NATIONAL SANATORIUMS*. *Kekkaku*, December, 1960, 35: 840–847. (*National Tokyo Sanatorium, Japan)

The effect of kanamycin on the postoperative course of lobectomy in patients with streptomycin-resistant tubercle bacilli was compared with that of streptomycin in patients with streptomycin-susceptible tubercle bacilli. Only those cases fulfilling the following criteria were included: only lobectomy was included in this series (segmental resection or pneumonectomy was excluded); the tuberculous cavity had to be more than 1 cm. in diameter; no active or infectious tuberculous lesion was present in the opposite lung; no bronchopleural fistula or empyema was present before operation; and the tubercle bacilli were completely resistant to 10 γ or more of streptomycin per ml. The conclusion was that kanamycin had a protective effect on the postoperative complications, and was useful in bringing about conversion of the sputum to noninfectiousness. A very good late result was obtained with kanamycin as well as with streptomycin in the control group consisting of patients with streptomycin-susceptible bacilli.—I. TATENO

Acoustic Disturbances Associated with Kanamycin Treatment of Pulmonary Tuberculosis (in Japanese). T. OKADA*, K. MATSUMURA, Y. ABE, and S. TANI. *Clin Resp Organs*, December, 1960, 12: 837–841. (*Institute for Infectious Diseases, Tokyo U., Japan)

Audiometric analysis was made of the acoustic disturbances in 30 patients who received kanamycin. The main symptoms were tinnitus and loss of hearing; the former appeared 3 to 4 or 9 to 12 months after kanamycin treatment was begun. The loss of hearing usually developed simultaneously with or after the tinnitus. The auditory disturbance was initially marked in the high-sound area (8,000 cycles per second), but with the progress of illness it became also recognizable in the low-sound area (6,000 and 4,000 c/s), indicating that it was an inner-ear type of disturbance such as occurs with streptomycin. The use of kanamycin in patients who had acoustic disturbances due to streptomycin aggravated the symptoms. The dosage schedule of kanamycin apparently had no effect on the incidence or time of onset of auditory disturbances. It was not possible to say that these side effects occurred less often with kanamycin than with streptomycin treatment. No drugs appeared to be effective in the treatment of the acoustic disorders.—I. TATENO

Drug Resistance of Tubercle Bacilli and Clinical Surgery. Reconsideration of the Problem (in Japanese). M. SHIOZAWA* and T. YOSHIDA. *Jap J Chest Dis*, January, 1961, 20: 23–29. (*Kekkaku Yobokai Institute, Kiyose, Japan)

The writers analyzed the factors which led to postoperative complications or the reappearance of tubercle bacilli in the sputum of patients who had drug-resistant tubercle bacilli preoperatively. It was concluded that the development of drug resistance was important to the surgeons only when the number of bacilli expectorated by the patient was large, and that the drug-resistant bacilli were of little importance when their number was small or when they disappeared before operation. The limit of drug susceptibility above which bacilli should be regarded as drug resistant

was 0.1γ of isoniazid per ml. and 10γ of streptomycin per ml. If one of the drugs is to be reserved so as to keep the bacilli from becoming resistant to it and thus be used effectively at the time of operation, streptomycin rather than isoniazid should be the drug reserved. The opinion that lobectomy rather than segmental lobectomy should be performed on drug-resistant patients was not uniformly acceptable. The type of operation should be dependent upon the amount of drug-resistant bacilli excreted by the patient. Thoracoplasty was a safe operation for drug-resistant patients but, if the distribution of the lesions permitted and an effective drug was reserved for operation, resectional surgery might be performed.—I. TATENO

Long-term Results of Chemotherapy in Pulmonary Tuberculosis in Children (in Japanese). K. HUKUSHIMA*. *Jap J Chest Dis*, December, 1960, 19: 839–843. (*Municipal Kiyose Children's Hosp., Japan)

During the past 10 years and 5 months, 1,265 children with pulmonary tuberculosis were discharged after they had received chemotherapy, and 644 children responded to the writer's inquiry as to their present status of health. Ten patients died and the illness became worse in 71 patients. Most of these retrogressive developments occurred within 3 years of discharge from hospital. The illness became worse in 10 per cent of the patients whose illness was classified as primary tuberculosis, and in 20 per cent of the patients with secondary tuberculosis at the time of admission to the hospital. Many patients who became worse had been discharged with unsatisfactory treatment, but there were some unfortunate patients who had been pronounced almost cured at the time of discharge. Tuberculosis in children, especially the secondary type, was considered to be closely related to the adult type of tuberculosis.—I. TATENO

Stevens-Johnson Syndrome, Erythema Multiforme Pluriorificialis, in Association with the Administration of Thiosemicarbasone. W. MOORE*. *Tubercle*, December, 1960, 41: 448–449. (*Mulago Hosp., Kampala, Uganda)

The Stevens-Johnson syndrome is considered to be a severe form of erythema multiforme, a toxic or allergic reaction to drugs or a foreign protein. The case described fits the category of a toxic sensitivity type of reaction to a specific drug; the fact that the symptoms stopped on the withdrawal of the drug, and recommenced when it was given again, clearly points to the etiologic role of thiosemicarbazone. The patient was successfully desensitized to the drug under protection of corticotropin, and was able to continue his treatment. No further reactions occurred. The importance of these observations lies in the fact that this reaction, and probably other toxic manifestations due to hypersensitivity to thiosemicarbazone, can be successfully overcome and the patient can continue his chemotherapy.—M. J. SMALL

Malignant Effusions Treated by Colloidal Radioactive Yttrium Silicate. J. WALTER*. *Brit Med J*, October 29, 1960, No. 5208: 1282–1284. (*U. of Sheffield, England)

As an alternative to radioactive gold in the treatment of malignant pleural and peritoneal effusions, the use of a new compound, colloidal radioactive yttrium silicate ($^{90}Y_2(SiO_3)_3$), is described. A preliminary report is given of its therapeutic use in 15 cases. Of 9 cases surviving more than 1 month, 6 had a good palliative result for 5 to 19 months. The advantages of yttrium over gold are discussed, especially the superior surface penetration of the beta-particles and the lesser radiation hazards owing to absence of penetrating gamma-radiation (after author's summary). —E. A. RILEY

The Medical Letter*. (*136 E. 57th St., N. Y.)

March 31, 1961, 3: 25–28: Surgicel®, Oxycel®, and Gelfoam®, absorbable hemostatic agents. The analgesic narcotic, piminodine ethanesulfonate (Alvodine®). Index to Vol. 3, pp. 1–24.

April 14, 1961, 3: 29–32: Results of laboratory tests of penicillin G tablets from 42 companies. The alcohol of pantothenic acid (Ilopan®) for postsurgical use.

PULMONARY PHYSIOLOGY

On the Relief of Bronchospasm and the Induction of Alveolar Hyperventilation. H. FROEB*. *Dis Chest*, November, 1960, 38: 483–489. (*Scripps Clinic and Research Foundation, La Jolla, Calif.)

Aerosol therapy with bronchodilator drugs has added much to the management of obstructive pulmonary insufficiency. Comparative studies of oral, parenteral, conventional inhalation and combined intermittent positive pressure breathing (IPPB) have not been conclusive. It was believed that information relating to arterial blood saturation, pH, and carbon dioxide tension might shed further light on the comparative effects of simple hyperventilation and IPPB with a bronchodilator. It was found that the relief of bronchospasm was the same with aerosols of isoproterenol whether administered by deep breathing or with IPPB. The degree of alveolar hyperventilation induced by the two methods seemed to be comparable, except for

the greater rise in arterial pH with IPPB. It is questioned whether this rise may represent a metabolic rather than a ventilatory effect. The increased alveolar ventilation induced by IPPB plays an important role in the mobilization of secretions and the distribution of the aerosol.
—E. A. ROUFF

The Determination of Carbon Monoxide Diffusing Capacity in Patients with Pulmonary Tuberculosis, and Its Clinical Significance (in Japanese). H. KANAGAMI*, T. KATSURA, K. SHIRAISHI, K. BABA, M. TANAKA, and A. MORI. *Jap J Chest Dis*, December, 1960, 19: 859–865. (*Kosankin Institute, Sendai, Japan)

The writers determined the carbon monoxide diffusing capacity (Dco) by Forster's single-breath method in 38 patients with pulmonary tuberculosis, and reached the following conclusions. (*1*) There was a moderate decrease in the resting Dco of 2 patients with active miliary tuberculosis. In 4 patients with the same disease, the ventilatory and intrapulmonary gas distribution functions returned to normal levels following successful chemotherapy, but the Dco remained subnormal. There was no parallel correlation between roentgenographic improvement and pulmonary functions, especially diffusing capacity of the lung. (*2*) The ventilatory and intrapulmonary gas distribution functions returned to normal in 12 patients with arrested pulmonary tuberculosis, but the oxygen coefficient remained high in 6 patients and the Dco remained depressed in 10. There was no correlation between the depressed diffusing capacity and the presence or absence of abnormal lung shadow. There was, however, a good correlation between the duration of the illness and diffusing capacity disturbances; the Dco was remarkably depressed in patients with illness of more than 3 years' duration, and less depressed in patients with illness of less than 3 years' duration. The Dco was depressed in proportion to the extent of the pathologic foci.—I. TATENO

Muscular Hyperplasia of the Lung: A Physiopathologic Analysis. F. GRAY, JR.* and A. FIELD, JR. *Ann Intern Med*, October, 1960, 53: 683–696. (*Yale U. School of Med., New Haven, Conn.)

Hyperplasia of the smooth muscle in the lung has been known to occur under pathologic conditions since 1872. The proliferated muscle is found in the walls of air passages, blood vessels, and lymphatics, as well as in the connective tissue of the alveolar septa and pleura. Bundles and sheets of smooth muscle may narrow or even obliterate air passageways as well as blood vessels, and a polyploid mass of hyalinized muscle may obstruct a major bronchus; thus, distention of pulmonary tissue and bullae formation occur. Muscular hyperplasia may be the primary cause of emphysema in some cases, and may be the explanation for the improvement occasionally experienced following the use of antispasmodic drugs in these cases. The reason for the increase in smooth muscle of the lung is not clear, although entrapment of muscle under increased tension could be a cause of hypertrophy. Organizing pneumonitis and the development of a rich collateral blood supply, chiefly venous, might contribute to smooth muscle proliferation. The formation of bullae involves compaction of lung tissue, with remnants of bronchiolar walls and their associated blood vessels giving rise to masses of residual smooth muscle. The clinical picture in 17 cases found in the literature is summarized. Five new cases are reported, with pathologic confirmation and extensive physiologic studies. The clinical picture is one of longstanding chronic cough, purulent sputum, dyspnea, cyanosis and, often, finger clubbing, with diffuse wheezes and fine rales throughout the lung fields. Physiologically, the difficulties consist of airway obstruction, impaired intrapulmonary gas distribution, and alveolar-capillary block. The process leads slowly but inexorably to cor pulmonale.
—T. H. NOEHREN

Physiologic Studies in Silicotic Patients Treated with Intermittent Positive Pressure Breathing (IPPB) and JB-251 (in Japanese). T. HUJITA*, H. EBIHARA, R. ITO, T. ASO, S. OTA, and M. KODAMA. *Clin Resp Organs*, December, 1960, 15: 847–851. (*Iwamizawa Rosai Hosp., Japan)

Fourteen silicotic patients were treated with IPPB and JB-251 (Caytine®) by aerosol for 10 minutes over a 30-day period, and the physiologic effects were analyzed. Shortness of breath, stridor, palpitation, cough, and sputum decreased in intensity or in volume, respectively. There were improvements in the vital, timed vital, and maximal breathing capacities, the ratio of the residual air volume to total lung volume, and the ventilation and air velocity indices. The increase in the maximal breathing capacity was most pronounced, and no untoward effects were observed. It is concluded that this treatment is effective in silicosis as it brought about improvements in subjective symptoms as well as in objective physiologic functions.
—I. TATENO

Estimation of Pulmonary Arteriovenous Shunt-Flow Using Intravenous Injections of T-1824 Dye and KR^{85}. H. W. FRITTS, JR.*, A. HARDEWIG, D. F. ROCHESTER, J. DURAND, and A. COURNAND. *J Clin Invest*, December, 1960, 39: 1841–1850. (*Columbia U. Division, Bellevue Hosp., N. Y.)

The intravenous injection of Kr^{85} dissolved in T-1824 dye provides a method for estimating the fraction of the pulmonary arterial blood flow perfusing arteriovenous shunts. As expected, large shunts were present in patients with Weber-Rendu-Osler's disease who exhibited arterial blood oxygen unsaturation. In contrast, no sizable shunts were evident in 8 patients with pulmonary emphysema or in 12 patients with pulmonary infections. Further, only small shunts were found in 14 patients with Laennec's cirrhosis, even though 9 of these patients had arterial saturations below 94 per cent. Additional studies on 5 of these patients suggested that vascular anastomoses connected the portal bed with the postcapillary segments of the pulmonary vessels. These studies did not reveal the size of the flow through the anastomoses, or whether this flow fully accounted for the reduced saturation of the arterial blood (Authors' summary).
—E. DUNNER

Effect of Tracheostomy Tubes on the Resistance to Breathing and Pulmonary Resistance in Patients with Poliomyelitis. B. G. FERRIS, JR.* and D. S. POLLARD. *New Engl J Med*, November 24, 1960, 263: 1048–1052. (*Harvard School of Public Health, Boston, Mass.)

Pulmonary resistance in the supine position in patients with poliomyelitis was shown to be increased compared with that observed in normal supine subjects. Breathing around tracheostomy tubes was shown to increase the upper-airway resistance: the larger the tube, the greater the effect. The presence of the tracheostomy tube could not account for all of the increase, however, and it was therefore suggested that variations in the pharyngolaryngeal pathway from voluntary or involuntary causes might explain the increased pulmonary resistance in patients with poliomyelitis. The increased pulmonary resistance seemed most likely due to gravity acting on the soft tissues of the oropharynx and larynx (after authors' summary).—M. J. SMALL

Pulmonary Mechanics. A Unified Analysis of the Relationship Between Pressure, Volume and Gasflow in the Lungs of Normal and Diseased Human Subjects. D. L. FRY* and R. E. HYATT. *Amer J Med*, October, 1960, 29: 672–689. (*Nat. Inst. of Health, Bethesda, Md.)

A three-dimensional graphic representation of the mechanical aspects of pulmonary ventilation has been developed from experimental data obtained in man, in which transpulmonary pressure, respiratory flow, and lung inflation have been uniquely related. The basic element of this representation is the isovolume pressure-flow curve. The behavior of a simple lung model is described to emphasize the general determinants of these isovolume pressure-flow curves. The broad inferences drawn from analysis of this model are applied to the pressure-flow-volume (P-F-V) relationship of the human lung. The three-dimensional surface representing the P-F-V relationship has had certain conceptual value. The concept of the αF-V curve evolved from consideration of this surface. This curve has been studied in man and found to have certain unique characteristics which suggest that it may become a valuable clinical tool. The αF-V curve is: quite reproducible, only moderately dependent upon effort, essentially unaffected by wide variations in upper airway resistance, determined by the physical properties and dimensions of the intrathoracic pulmonary system, greatly altered in emphysematous subjects, and relatively easily obtained.—T. H. NOEHREN

Respiratory Mechanics During Forward Acceleration. J. F. WATSON*, N. S. CHERNIACK, and W. ZECHMAN. *J Clin Invest*, November, 1960, 39: 1737–1743. (*Biomedical Lab., Wright-Patterson Air Force Base, Ohio)

The respiratory mechanics of forward acceleration were studied in 4 normal subjects who were experienced in riding the free-swinging cab of a human centrifuge. All of the lung volumes decreased proportionately, with the exception of residual volume, which became a larger fraction of the total lung capacity. The resting midpulmonary position decreased. As acceleration increased, intrapulmonary pressure increased for a constant volume, shifting the relaxation pressure-volume curve downward and to the right. Static and dynamic total pulmonary compliances decreased as a result of the decrease in functional residual capacity. Elastic work approximately doubled, due to the work necessary to overcome acceleration resistance. Nonelastic work did not change. Inspiration during 4-G acceleration was active regardless of the end-expiratory position. It is suggested that respiratory mechanics during forward acceleration and negative pressure breathing are similar.
—E. DUNNER

MICROBIOLOGY AND IMMUNOLOGY

***Moraxella Duplex Nonliquefaciens* in Bronchial Secretions** (in Hungarian). G. BERENCSI* and G. Mészános. *Tuberkulozis*, June, 1960, 6: 174–175. (*U. of Debrecen, Hungary)

This bacterium is a pleomorphous gram-labile organism which appears in culture (beef blood–agar or bouillon agar) either as a diplobacillus or resembling staphylococci or streptococci. It was

present in 36 cultures of 455 bronchial secretions examined. It is noteworthy that 91 secretions obtained from patients with bronchiectasis yielded the greatest number of positive cultures (21) (23.08 per cent). The pathogenicity of this microorganism is as yet unknown.—Z. VIRÁGH

Methods for the Grouping and Typing of Mycobacteria. I. JUHLIN*. *Acta Path Microbiol Scand*, No. 2, 1960, 50: 177–270. (*U. of Lund, Sweden)

1. Differentiation of Mycobacteria into *M. Tuberculosis* and Anonymous Mycobacteria: pp. 177–187.

By means of a salicylate effect test, isoniazid-resistance determination, and the catalase activity test, a grouping of mycobacteria into *M. tuberculosis* and unclassified mycobacteria may be made.

2. Differentiation of *Mycobacterium Tuberculosis* into *Typus Humanus* and *Typus Bovinus*: pp. 188–194.

By means of the Peknice and Asmus-Garschagen niacin tests and resistance tests against thenoyl-2-hydrazine and furfuroyl-2-hydrazine, *M. tuberculosis* can be grouped into the human and bovine strains. A test for transhydrogenase activity also makes it possible to classify *M. tuberculosis typus bovinus* into bovine strains and BCG strains. In addition, a comparison with the results obtained from salicylate-effect tests and catalase-activity tests and resistance testing against isoniazid gives further evidence as to whether the strain investigated belongs to *M. tuberculosis* or to the unclassified mycobacteria.

3. Differentiation of Anonymous Mycobacteria into Groups, Sub-Groups or Types: pp. 195–270.

The nicotinamidase test is a generally useful and accurate method for differentiating *M. tuberculosis typus humanus* from the *typus bovinus* and BCG strains. Occasional old bovine laboratory strains and certain BCG strains which are difficult to distinguish from human strains by means of the niacin test and the resistance test against thenoyl-2-hydrazine and furfuroyl-2-hydrazine can be differentiated by the nicotinamidase test.
—E. DUNNER

Synthesis of Nicotinic Acid by *Mycobacterium Tuberculosis* (in German). A. NELLES* and H. HERSCHMANN. *Tuberkulosearzt*, December, 1960, 14: 813–820. (*Tbk.-Klinik, Bad Berka, Germany)

The synthesis of nicotinic acid by *M. tuberculosis* was studied. All of the strains (45 human, 3 saprophytic, 5 bCG, and 1 H37Rv) were cultured on various media for 40 to 50 days. The nicotinic acid content of the medium was then determined colorimetrically by König's reaction. The smallest quantity that could be estimated by this method was 1 γ per ml. Except for the saprophytic strains, all of the strains studied produced nicotinic acid, the largest quantity being formed in a modified Sauton medium. Nicotinic acid synthesis by the human strain was highest in media containing 1 per cent asparagine and 1 per cent glycerin. The optimal conditions for BCG strains were at concentrations of 1 per cent asparagine and 0.75 per cent glycerin. Repeated subcultures had no effect on the quantity of nicotinic acid synthesized by individual strains.—J. HAAPANEN

Tubercle Bacilli Research on Petragnani Medium from 1948 to 1959: A Statistical Study of 15,075 Cases (in Italian). T. ROSSI* and A. STAFFA. *Ann Med Sondalo*, No. 1, 1960, 8: 31–38. (*Villaggio Sanatoriale, Sondalo, Italy)

A simple statistical evaluation is given of the results obtained between 1948 and 1959 using Petragnani medium for isolation of tubercle bacilli. The incidence of positive reactions among 15,075 samples (sputum, gastric juice, pleural fluid, bronchial secretions, et cetera) was 16 per cent. The highest percentages were obtained from pleural fluid (23.7 per cent) and bronchial secretions (22.8 per cent). No substantial difference was found between the results before and after isoniazid was normally employed in treatment, 14.5 and 16.4 per cent, respectively. The contamination rate was very low (1.9 per cent) and it was present particularly when endocavitary material was cultured. According to these results, it is claimed that Petragnani medium, with 2 per cent malachite green, is still a good method for the isolation of tubercle bacilli.—I. ARCHETTI

The Effect of Anthranilic Acid on the Growth of Tubercle Bacilli (in Japanese). M. KAGAMIYAMA* and M. MAJIMA. *Kekkaku*, December, 1960, 35: 868–871. (*Kenkohoken Hoshigaoka Hosp., Kansai, Japan)

Most of the antituberculosis compounds are foreign and nonphysiologic substances. The present authors studied the antituberculous activity of anthranilic acid, which is a physiologic metabolite of tryptophane in the human body. This compound was selected in view of its structural similarity to PAS. The minimal growth-inhibiting concentration of anthranilic acid against the H37Rv strain of tubercle bacilli in Dubos medium was 500γ per ml. (pH 7.0), and 250γ per ml. (pH 6.0). The Takeo strain of avian tubercle bacilli was inhibited at 750γ per ml. (pH 6.0). The anthranilic acid had inhibitory action on the glutamic-acid metabolism of the living cells, i.e., it blocked the activity of

glutamic decarboxylase. This effect was considered one of the important mechanisms of the antituberculous activity of anthranilic acid.—I. Tateno

Contribution to the Study of Bacterial Multiplication. Acidophilic Bacilli (in French). J. Degommier*. *Ann Inst Pasteur (Par)*, November, 1960, 767–776. (*Institut Pasteur, Paris, France)

Mycobacterium tuberculosis is generally considered a basophilic, acid- and alcohol-resistant organism. If an acid stain is correctly applied to a pure culture, however, a small number of bacilli are seen (1 per cent) which are colored only by acid stains. The author has classified them as "acidophilic," in contrast to "basophilic." Their biologic significance may be explained by 2 hypotheses: (*1*) every bacillus passes through a transitory acidophilic stage; (*2*) a mode of multiplication different from the usual scissiparity exists for a small number of bacilli, and this group would develop differently and acquire different specific characteristics.—V. Leites

Mailing of Infectious Specimens for Diagnostic Purposes. U. P. Kokko*, J. Stuart, and G. Taylor. *Public Health Rep*, November, 1960, 75: 979–984. (*Communicable Disease Center, U.S.P.H.S., Atlanta, Ga.)

EXPERIMENTAL PATHOLOGY

A Study of the Bronchial Mucous Glands in White South African Gold Miners. A Histological Survey. C. B. Chatgidakis*. *AMA Arch Environ Health*, October, 1960, 1: 335–342. (*South African Inst. for Med. Research, Johannesburg)

Enlarged mucous glands showing excessive secretion with dilatation of the ducts is the characteristic lesion of chronic nonspecific bronchitis. An histologic survey was made of the bronchial mucous glands in white gold miners and in a control group of white nonminers, both male and female. It was shown that enlarged bronchial mucous glands with excessive mucous secretion and dilated ducts are much more common in males and, apparently, age in itself does not affect them. The results suggest that enlarged bronchial glands with excessive mucous secretion and dilated ducts occurred with increased frequency as the silicosis became more severe. But this was also found to be true with great frequency in elderly male nonminers, and the miner with silicosis is an aging male who is subject to all of the usual nonindustrial bronchial diseases. In addition, he is a heavy smoker. The bronchi of 15 nonsmoking gold miners with various degrees of silicosis were examined, and it is suggested that silicosis in itself plays no part in the enlargement of the bronchial mucous glands. There appears to be no increased incidence of enlarged mucous glands in the bronchi in patients with acute pneumonia and tuberculosis. No consistent qualitative alteration in the mucus secreted in normal control subjects, in persons with nonspecific chronic bronchitis, or in the bronchi of miners with various degrees of silicosis could be detected by any of the methods employed.
—T. H. Noehren

A Comparison of the Cell Block, Papanicolaou, and Millipore Filter Technics for the Cytologic Examination of Serous Fluids. P. D. Taft* and J. M. Arizaga-Cruz. *Amer J Clin Path*, December, 1960, 34: 561–564. (*Harvard Med. School, Boston, Mass.)

The diagnosis of malignant neoplasms from sediments of serous effusions cannot only be made with greater accuracy if 2 methods are used, but the number of specimens on which no diagnosis can be made may be reduced. If a single method is to be used, the cell-block and the Millipore-filter techniques yield comparable results and are better than the Papanicolaou smear. The Millipore-filter technique is especially useful for small amounts of fluid and for fluid containing blood.
—E. Dunner

The Development of Positive Serologic Tests with *Histoplasma Capsulatum* Antigens Following Single Histoplasmin Skin Tests. S. C. McDearman* and J. M. Young. *Amer J Clin Path*, November, 1960, 34: 434–438. (*V.A. Hosp., Memphis, Tenn.)

A single histoplasmin skin test can stimulate the development of humoral antibodies that can be demonstrated with *Histoplasma capsulatum* antigens. The practical significance of these findings is obviously the interpretation of serologic results following the administration of histoplasmin skin tests, even a single skin test. The suggestion is made, with some supportive evidence but certainly without proof, that the development of certain antibodies following a single histoplasmin skin test indicates a minimally active fungous infection.—E. Dunner

The Nature of the Neonatal Pulmonary Hyaline Membrane. R. A. Barter* and T. G. Maddison. *Arch Dis Child*, October, 1960, 35: 460–464. (*Royal Women's Hosp., Melbourne, Australia)

The authors studied a very large series of cases of hyaline membrane disease in the newborn to determine the nature and origin of the membranes. They examined 133 consecutive newborns who came to necropsy and the clinical histories were

concurrently reviewed. The majority died within 16 hours of birth: 123 were premature infants; 60 per cent were asphyxiated at birth. Detailed microscopic study of the lungs showed that the membranes resulted from epithelial cell necrosis in the respiratory bronchioles and formed *in situ*.
—J. LORBER

Pulmonary Toxoplasmosis. Experimental and Clinical Facts (in French). M. PERRIN-FAYOLLE* and J. P. GARIN. *Presse Med*, November 23, 1960, 52: 1994–1997. (*Faculty of Medicine of Lyons, France)

Experimental pulmonary toxoplasmosis was studied from the clinical and pathologic points of view in 50 mice. The inflammatory changes are described in detail. A number of the mice were treated with "sulfamethopyrazin" and "spiromycine-trisulfazine" with not entirely satisfactory results. Pulmonary toxoplasmosis in humans has been encountered mostly as part of a septicemic disease which is usually fatal. One case of isolated pulmonary toxoplasmosis is reported; this patient recovered spontaneously.—E. LYON

Modified Pathogenicity and Virulence of Tubercle Bacilli Embedded in Liquid Paraffin. I. Human Tubercle Bacilli (in Japanese). K. DOI*. *Kekkaku*, November, 1960, 35: 738–742. (*Tuberculosis Institute, Kyoto U., Japan)

Strain H37Rv, the less-virulent F strain, and the H37Ra strain of tubercle bacilli were embedded in liquid paraffin and 10 mg. of each were inoculated intraperitoneally into mice. The survival time of the animals was compared with that of mice which were inoculated with untreated tubercle bacilli of the same strains. The survival time of the mice inoculated with the virulent paraffin-embedded H37Rv strain was longer and the pathologic lesions were fewer than in the mice inoculated with untreated bacilli. A reverse phenomenon was observed when the F strain was inoculated. The paraffin-embedded H37Ra strain had a tendency to multiply in the organs of mice, although they survived, as did the control group. The virulence of the virulent strain was apparently reduced, while that of the less virulent strain was considerably enhanced by embedding the bacilli in paraffin. It was also found that the virulent bacilli were able to multiply within the cells but not in the body fluid, while the reverse was true for the less virulent bacilli.—I. TATENO

Modified Pathogenicity and Virulence of Tubercle Bacilli Embedded in Liquid Paraffin. II. Bovine Tubercle Bacilli (in Japanese). K. DOI*. *Kekkaku*, December, 1960, 35: 831–834. (*Tuberculosis Institute, Kyoto U., Japan)

When 10 mg. of the virulent Ravenel strain of bovine tubercle bacilli suspended in liquid paraffin were inoculated into mice intraperitoneally, the bacilli were distributed in the organs, they adsorbed to the particles of liquid paraffin, and their multiplication *in vivo* was considerably reduced. The formation of lesions was retarded, and the inoculated mice survived longer than those inoculated with the same strain of tubercle bacilli suspended in saline. In contrast, the multiplication of the less virulent RM and BCG strains inoculated in liquid paraffin suspensions was considerably greater in the organs, and the mice died earlier with hemorrhagic lesions than those inoculated with saline suspensions of the bacilli. These results showed that, when the bovine bacilli were embedded in liquid paraffin, the pathogenicity and virulence of the virulent strain were decreased while those of the less virulent or avirulent bacilli were increased; this served as confirmation of the writer's work with human tubercle bacilli.—I. TATENO

The Fate of Inhaled Particles in the Early Postexposure Period. II. The Role of Pulmonary Phagocytosis. C. W. LABELLE* and H. BRIEGER. *AMA Arch Environ Health*, November, 1960, 1: 423–427. (*Jefferson Med. College, Philadelphia, Penn.)

A significant proportion of an inhaled dose of insoluble particulates is expelled from the lung within the first 24 to 48 hours following inhalation. The actual fraction of the total dose expelled during this early postexposure period can be altered at will by increasing the total lung burden through the addition of inert particles to the primary load of radioactive particles. When the lungs of the animals are examined histologically, a significant correlation exists between the percentage of the dose that is cleared and the number of phagocytic cells that can be counted in a standard section of lung. A method is described by which the number of free phagocytic cells in the lungs of rats can be estimated. It is concluded that transport of deposited particles by phagocytes is the primary mechanism by which inhaled dust particles are eliminated from the lung following inhalation.—T. H. NOEHREN

The Properdin Level in Pulmonary Tuberculosis (in French). P. VULLIÉMOZ* and G. FAVEZ. *Schweiz Z Tuberk*, No. 4, 1960, 17: 286–290. (*Clinique Sylvana, Epalinges VD, Switzerland)

The properdin level in the blood was determined at intervals in 54 patients with various forms of pulmonary tuberculosis. No correlation was found between the severity of the tuberculous process and the properdin level.—Z. VIRÁGH

Proteinpolysaccharides of Human Costal Cartilage. B. JOHNSON* and M. SCHUBERT. *J Clin Invest*, November, 1960, 39: 1752–1757. (*New York U. School of Med., N. Y.)

A study of human costal cartilage was made which employed the extraction procedure developed for use with bovine nasal cartilage. By 3 successive extractions with water, crude proteinpolysaccharide was isolated in amounts of 20 to 35 per cent of the dry weight of the cartilage. While similar in properties to the crude proteinpolysaccharide reported from bovine nasal cartilage, the corresponding product from human costal cartilage contained more protein and less polysaccharide. Ultracentrifugal fractionation at 78,000 × G resulted in separation of this crude product into a rapidly sedimenting fraction and a nonsedimenting fraction. Both fractions contained more protein than did the corresponding fractions made from bovine nasal cartilage.
—E. DUNNER

Pathological Changes Associated with the Inhalation of Sodium Zirconium Lactate. J. T. PRIOR*, G. A. CRONK, and D. D. ZIEGLER. *AMA Arch Environ Health*, October, 1960, 1: 297–300. (*Upstate Med. Center, Syracuse, N. Y.)

Six albino rabbits were subjected to 44 per cent sodium zirconium lactate mist daily for 6 weeks. Each exposure lasted 20 minutes. Pathologic examination at the end of the 6 weeks revealed that all of the test animals had either bronchiolar abscesses with a lobular type of pneumonia, or peribronchial granulomas. An extrapulmonary granuloma was found in the tongue muscle of 1 animal. Six control animals killed after 6 weeks were free from gross or histologic infections or granulomas. Previous contacts with sodium zirconium lactate did not intensify the pulmonary reaction (after authors' summary).—T. H. NOEHREN

Study on the Multiplication of the H37Ra Strain *in Vivo* and the Resultant Induction of Tuberculin Allergy in Guinea Pigs. A Note on the Effect of Combined Inoculation of the H37Ra and the BCG Strains of Tubercle Bacilli (in Japanese). M. TOYOHARA* and Y. OBAYASHI. *Kekkaku*, December, 1960, 35: 857–860. (*Kekkaku Yobokai Institute, Kiyose, Japan)

The behavior was studied of streptomycin-resistant H37Ra and BCG strains of tubercle bacilli inoculated intravenously in guinea pigs singly or in combination. The livers, lungs, and spleens were quantitatively cultured for tubercle bacilli following inoculation. When both strains were injected, the speed of the multiplication and the number of bacilli at the peak period (2 weeks after inoculation) were greater for both strains than when they were inoculated singly, i.e., a synergistic action was observed. However, the BCG strain survived longer than was the case with single inoculation. This was considered to be an interference phenomenon favoring the more virulent H37Ra strain over the BCG strain. A strong tuberculin reaction was observed with both the single and combination inoculations.—I. TATENO

PUBLIC HEALTH AND EPIDEMIOLOGY

Air Contamination and Chronic Bronchitis (in Japanese). Y. NOSE*. *Saishin Igaku*, August, 1960, 15: 2056–2067. (*Yamaguchi Med. College, Japan)

Although the incidence of bronchitis is influenced by environmental factors, its development and the clinical course until the death of the patient are dependent to some extent upon the resistance of the host. The death rate from bronchitis has a positive correlation with the mean temperature of the year, and a negative correlation with the yearly precipitation: it is high in tropical, temperate, and cold zones, in this order. This may mean that the high incidence of bronchitis in cold zones results in the immunity of the population in general and, thus, in a low death rate; but the high tropical death rate may also be due to the low social and cultural standards associated with poor medical facilities and geographic factors related to soil or plant life which result in poor nutritional and hygienic standards. Air contamination and the incidence of bronchitis are closely related, and the concentration of sulfuric oxide or its reaction products with other minerals and solid materials in the air have an acute or chronic influence on the course of bronchitis. But the difference in the incidence of and death rate from bronchitis in the industrial areas of varied geographic distribution indicates that the resistance of the host and other environmental factors, in addition to the nature and concentration of air contaminants, are at work in the development of bronchitis.—I. TATENO

Air Pollution and Respiratory Disease. A Preliminary Report. F. C. DOHAN* and E. W. TAYLOR. *Amer J Med Sci*, September, 1960, 240: 337–339. (*U. of Pennsylvania School of Med., Philadelphia)

Analysis of epidemiologic data obtained from insurance and personnel statistics of a large multiplant electronics company demonstrates a high correlation between the average concentration of an air pollutant (particulate sulfates) and the in-

cidence of respiratory diseases lasting more than 7 days in women working in 5 cities. The high statistical correlation does not prove a causal relationship; however, it is believed that the evidence presented, plus the well-known irritating effects upon the respiratory tract of sulfur dioxide and sulfurous and sulfuric acid in higher-than-usual concentrations in the air, suggest that these, or derivatives, may increase individual susceptibility to common infectious respiratory diseases. It is also believed possible that air pollution with sulfates may increase the duration of acute respiratory diseases.—W. J. STEININGER

The Arsenic Content of Bronchial Mucosa and Submucosa in Man. A Comparison of Specimens from Lung Cancer Victims and Control Tissue. R. H. HOLLAND*, A. R. ACEVEDO, and D. A. CLARK. *Brit J Cancer*, June, 1960, 14: 169–172. (*V.A. Hosp., Dallas, Texas)

Recent evidence has shown a high arsenic concentration in urban atmospheres (the result of carbonaceous combustion) and a 200 to 600 per cent increase in the arsenic content of most American cigarette tobaccos from 1932 to 1957. Inhaled arsenic is, therefore, under investigation as an environmental cause of lung cancer. In this study, analysis was made of the arsenic content of the bronchial mucosa and submucosa from 15 lung cancer victims, and from 23 cadavers which showed no evidence of neoplastic disease in the respiratory system. The mean value for As_2O_3 in the lung cancer tissues (7.14γ per gm.) was significantly higher than in the control group (4.13γ per gm.). It appears that 5γ or more of As_2O_3 per gm. of wet bronchial mucosa and submucosa are an excessive amount. Inhaled arsenic is believed to be the most important causal agent of lung cancer.
—W. J. STEININGER

The Arsenic-Poisoning Epidemic of 1900: Its Relation to Lung Cancer in 1960—An Exercise in Retrospective Epidemiology. H. S. SATTERLEE*. *New Engl J Med*, October 6, 1960, 263: 676–684. (*Newport, New Hampshire)

The renowned epidemic of arsenic poisoning that occurred among beer drinkers of the Manchester-Salford-Liverpool district of England in the autumn of 1900 remains an historic instance of mass poisoning by mechanisms which are of special concern today. In 1960, it is sobering and edifying to reflect that a national challenge to British public-health administration was capable of evoking a competent and well-organized inquest that promptly discovered and recorded new facts and resolved conflicting opinions and doctrines in a way that at once promoted harmony and a constructive solution to the problem. By contrast, it is depressing to contemplate present-day inertia in the smoking-cancer problem, frustrated in a tangle of controversy and mixed motivation, without prospect of the authoritative organization and coordination of action that its solution demands. The modern problem of lung cancer in cigarette smokers and in urban populations seems to be confused and prejudged by unsupported assertions that repudiated or ignored the cocarcinogenic effects of catalytic trace concentrations of arsenic in occupational and experimental tar cancer in the years 1919–28. A new emphasis on arsenic as a logical suspect for a significant carcinogenic component of cigarette smoke stems from the work of Holland *et al.* On the other hand, arsenic is regarded as a ubiquitous contaminant of all human atmospheric environments: it has yet to be recognized and estimated by realistic methods of air sampling, and is thus still minimized or ignored by industrial toxicologists and public-health hygienists in the United States. In England, however, arsenic has lately been reaffirmed in both of these roles by the posthumous publication of Sir Ernest Kennaway's article, written in collaboration with Professor A. J. Lindsey. In this discussion, arsenic and benzpyrene are rated together as the most prominent carcinogenic agents "common to coal smoke and cigarette smoke." These two eminent authorities sagely conclude that their "summary of existing knowledge of possible exogenous factors in connection with lung cancer demonstrates the need for fuller chemical investigation of tobacco, tobacco smoke, and town air."
—M. J. SMALL

Reactions to Influenza Vaccine Inoculations. J. LYNCH*, M. FOX, W. THAYER, and G. SCHMIT. *AMA Arch Industr Health*, June, 1960, 21: 574–578. (*National Inst. of Health, Bethesda, Md.)

In the fall of 1957 and again in 1958, inoculation against influenza was offered by the Employee Health Service of the National Institutes of Health on a voluntary basis to all employees. Recalling previous influenza immunization programs, many persons were concerned that the inoculations might cause more disability in terms of absenteeism and reduced working efficiency than the disease itself might produce. The present study was designed to obtain data on the nature and extent of reactions to influenza inoculations, using two different strengths of Asian strain vaccine and the 1958 polyvalent vaccine. Local and systemic reactions to 4,699 influenza vaccine inoculations given to National Institutes of Health employees were studied. Reactions were not excessive or severe and were not considered to have adversely influenced the over-all working efficiency or productivity of the staff.—T. H. NOEHREN

The Incidence of Malignant Disease in 1,620 African (Bantu) Gold Miners. C. CHATGIDAKIS*. *Arch Environ Health*, July, 1960, 1: 17–19. (*S. African Inst. for Med. Research, Johannesburg)

The autopsy incidence of malignant disease in 1,620 African male gold miners was found to be 6.3 per cent. Primary carcinoma of the liver was the commonest type found, 72 per cent of all malignancies. The over-all incidence of primary lung cancer was 0.3 per cent and formed 4 per cent of all malignancies. The presumptive conclusions are: (*1*) that the incidence of primary lung cancer is low in the African male, and (*2*) that neither silicosis nor underground service are factors in the production of primary cancer of the lung.
—T. H. NOEHREN

Asthmatic Factors in Chest Complaints of Miners. K. DE VRIES*, N. G. M. ORIE, and A. V. M. MEY. *Acta Med Scand*, July 15, 1960, 167: 301–308. (*University Hosp., Groningen, Holland)

On the basis of 2 groups of children, asthmatic and nonasthmatic, 2 groups of miners were formed: an "asthma" group, consisting of relatives of the asthmatic children, and a control group of relatives of nonasthmatic children. The incidence of chest complaints and roentgenographic changes in both groups was compared. It was concluded that an asthmatic predisposition is an important factor in the pathogenesis of chest complaints of miners. The underground work also influences the incidence of these signs and symptoms. It may be regarded as a provocative factor acting on the asthmatic predisposition. The influence of anthracosilicotic changes on the incidence of chest complaints could not be demonstrated.—E. DUNNER

Occupational Disease in California Attributed to Pesticides and Agricultural Chemicals. G. KLEINMAN*, I. WEST, and M. AUGUSTINE. *Arch Environ Health*, August, 1960, 1: 118–124. (*California State Dept. of Public Health, Berkeley)

Under the California Labor Code, each physician who attends an injured employee as well as the employer of that injured person are required to file a report with the California State Department of Industrial Relations if the disability lasts beyond the day of injury and requires more medical service than ordinary first aid. Since injury as defined in the Labor Code includes illness, the California State Department of Public Health has arranged with the Department of Industrial Relations to analyze the reports submitted for 1957 which involve occupational disease (attributed to pesticides and agricultural chemicals). These physicians' reports are the source of the data analyzed in this paper. Physicians recorded dermatitis on 55 per cent of the reports, systemic poisoning on 34 per cent, respiratory illness on 8 per cent, and other and unspecified diagnoses on 4 per cent.
—T. H. NOEHREN

Occupational Health Studies of the Shell-Molding Process. G. TUBICH*, I. DAVIS, and B. BLOOMFIELD. *AMA Arch Industr Health*, May, 1960, 21: 424–444. (*Michigan Dept. of Health, Lansing)

The shell-molding process was developed in Germany by Johannes Croning during the latter part of World War II. It is said to be the first major change in foundry practice principles since the Bronze Age and, although refinements have been produced over the centuries, none have effected a basic process change of such importance. While not applicable to large, heavy castings, the shell process does play a big part in the production of small and medium-sized mass-produced castings. Since its introduction, many hundreds of foundries throughout the world have incorporated this process into their production lines. It is estimated that in the United States approximately 25,000 workers are employed in shell molding. The shell-molding process does not reduce dust concentrations in the foundry environment. Forty-five per cent of the dust concentrations exceed 20 million particles per cubic foot of air. Free silica content of molding materials and air-borne dust and the particle size are similar in both shell-molding and conventional foundry operations. A series of drawings is presented to show how specific dust and solvent-vapor problems may be controlled.
—T. H. NOEHREN

Massive Pneumoconiosis from a Rock Dust Containing No Free Silica. H. BARRIE* and L. GOSSELIN. *Arch Environ Health*, August, 1960, 1: 109–117. (*U. of Toronto, Canada)

Nepheline rock consists mainly of the feldspar albite and is a plutonic rock. The presence of nepheline syenite in it is an indication that during its formation no free silica was present. It is hard and consists of mixed sodium, potassium, and aluminum silicates. Deposits of nepheline rock are not very common and may be white or grey, any color in them being due to the presence of metallic impurities. In industry, the rock is milled to a fine powder which is used for producing glazes on pottery. A man who had been exposed to nepheline rock for 4 years was necropsied 6 years after exposure had terminated, and was found to have a massive pneumoconiosis. Where simple depositions of dust were present in the lungs they were found in the lymphatic pathways, and had caused formation of reticulin fibrils but negligible collagen. The areas of massive pneumoconiosis showed the addi-

tional feature of organizing inflammatory exudates and severe obliterating endarteritis of the pulmonary vessels. Some of the lesions may have been due to the fact that albite forms long crystals which might be mechanically irritating. The inflammatory exudates were attributed to nonresolution of episodes of bronchopneumonia.
—T. H. NOEHREN

The Health of Workers in a Plant Making Highly Dispersed Silica. H. VOLK*. *Arch Environ Health*, August, 1960, 1: 125–128. (*State Board of Health, Rhein, Germany)

In their plant at Rheinfelden/Baden, the German firm Degussa, of Frankfurt/Main, has been producing since 1944 a highly dispersed chemically pure silica under the trade name of Aerosil®. A special method is employed by which the silica is produced at high temperature in the gas phase. By the hydrolytic decomposition of pure silicon tetrachloride in an oxyhydrogen flame, a product is obtained which consists of extremely small, spherically-shaped, primary particles (5–40 μ). The oxide is finding abundant application in the rubber and plastics industries; in the manufacture of lacquers, paints, and printing inks; in the pharmaceutical and cosmetic industries; in glues and lubricating grease; in the manufacture of electric light bulbs, fluorescent tubes, floor wax, automobile polish, and cellophane; and as a constituent for vacuum powder insulators. It can be stated that during 14 years of observation of the employees of this silica plant (215 workers), there was not a single case in which a suggestion of silicosis could be seen.—T. H. NOEHREN

A Sociomedical Study of the Mortality in Merchant Seafarers. A. OTTERLAND*. *Acta Med Scand*, May 20, 1960, 167: Supp. 357, 5–300. (*U. of Göteborg, Sweden)

An analysis of 2,014 deaths in the population of active seafarers registered in Sweden from 1945–1954 showed that the mortality was more than twice as great among active Swedish seafarers as among nonseafaring Swedish men of the same age during the same period. The mortality from tuberculosis has not decreased at the same rate among seafarers as it has among the male population as a whole. Neoplasms occurred at about the same rate among seafarers as among the other male population. The mortality from neoplasms was greater among the personnel of engine-room and catering departments than among men engaged on deck, and greater among officers than among enlisted men.—E. DUNNER

Enamel Pneumonoconiosis (in German). J. ERDÉLY* and A. ÖKRÖS. *Fortschr Roentgenstr Nuklearmed*, March, 1960, 92: 235–246. (*U. of Budapest, Hungary)

When first examined in 1939, a 36-year-old woman gave a history of working with an enamel spray gun for 14 years. Masks and ventilation were not used adequately at her place of employment. After 4 years of employment, she noticed frequent episodes of bronchitis. After 12 years, dyspnea and chest pain occurred frequently. The chest roentgenogram showed submiliary nodules in both mid- and lower-lung fields, and egg-shell calcification in the hilar nodes. Although the patient discontinued her work in 1939, re-examination in 1952 showed marked progression in both lung fields with further enlargement of the hilar densities. When seen again in 1957, she was physically incapacitated, the lung lesions had again increased, and the right heart was enlarged. The patient died in 1958 following appendectomy and heart failure. On macro- and microscopic examinations it was seen that the enamel particles had penetrated the alveolar walls. In the interstitial tissue, they were absorbed by fixed and mobile cells and transported to the peribronchial nodes. There was marked pulmonary fibrosis and thickening of the vascular channels. Some macrophages filled with enamel dust had migrated back into the alveolar space.—H. ABELES

Chemoprophylaxis During Respiratory Infections in a Private Pediatric Practice. E. H. TOWNSEND, JR.* *AMA J Dis Child*, May, 1960, 99: 566–573. (*26 S. Goodman St., Rochester, N.Y.)

A study was made of the use of antimicrobial agents to prevent secondary infections during respiratory illnesses by the random selection method in a private pediatric practice. The results indicate that there is no benefit to be gained from the routine use of these agents, even when a therapeutic dosage schedule is followed. In this study the physician, although adhering to the random selection method, knew to which program the individual patient was submitted. An attempt to reduce any resultant prejudice was constantly kept in mind, but the more desirable "double blind" method is planned in an attempt to answer any objections arising from this.—M. J. SMALL

Epidemiologic Methods in the Study of Silicosis. H. PARRISH* and H. ASHE. *Arch Environ Health*, August, 1960, 1: 129–139. (*Marion County Gen. Hosp., Indianapolis, Ind.)

Silicosis is described as a long-term, chronic illness which can be studied using methods and techniques of modern, chronic disease epidemiology. The Vermont granite industry is used to illustrate some of these epidemiologic principles.
—T. H. NOEHREN

Comparison of Smokers and Nonsmokers. I. A Preliminary Report on the Ability to Taste Phenylthiourea (P.T.C.). C. B. Thomas* and B. H. Cohen. *Bull Johns Hopkins Hosp*, No. 4, 1960, 106: 205–214. (*Johns Hopkins U. School of Med., Baltimore, Md.)

To determine possible constitutional differences between smokers and nonsmokers, studies were undertaken to explore the frequency of several genetic traits among groups of healthy subjects. This report presents findings with respect to taste-sensitivity to phenylthiourea (P.T.C.). Blood-bank donors, 597 white and 232 Negro males, were given a standardized taste test with filter paper impregnated with P.T.C., and were interviewed as to smoking habits. Among both the white and Negro men, cigarette smokers showed a higher proportion of tasters than did nonsmokers.—C. H. Pierce

Smoking and Chest Disease. Report of the Joint Tuberculosis Council of Great Britain*. *Tubercle*, August, 1960, 41: 290–301. (*Hawkmoor Chest Hosp., Bovey Tracey, Devon, Eng.)

In the past few years, evidence has been accumulating that, in 2 common forms of chest disease—cancer of the lung and chronic bronchitis—smoking is an important etiologic factor; it may also play a part in a third form: pulmonary tuberculosis. With this in mind, the Council has produced this report. The Joint Tuberculosis Council is an independent voluntary body composed of representatives of various medical societies throughout the country which have an interest in tuberculosis and other diseases of the chest. The conclusions of this report are as follows: (*1*) There has been a great increase in cigarette smoking during the last 50 years. (*2*) Smoking, particularly of cigarettes, impairs efficient ventilation of the lungs in healthy persons. (*3*) Cigarette smoking is the major factor accounting for the increased incidence of cancer of the lung; it may possibly act in association with other factors, such as air pollution. (*4*) There is a strong association between chronic bronchitis and cigarette smoking, although other factors, such as air pollution, also have an important etiologic influence on this disease. (*5*) Cigarette smoking is possibly a cause of the breakdown of healed or quiescent respiratory tuberculosis. Further work is required to confirm or refute this possibility. (*6*) A more active policy designed to reduce the amount of cigarette smoking is required. Greater publicity is necessary concerning its effects, and more effort on a national and personal scale should be given to solution of the many associated problems. (7) Special efforts should be made to discourage young people from taking up smoking. (*8*) In particular, members of the medical profession should, by example and by persuasion, assist their patients and others to reduce or abandon cigarette smoking. —M. J. Small

A Tuberculin Survey in a Large Urban Area. A. H. Griffith*, M. J. Bellamy, and J. K. McFarlane. *Tubercle*, August, 1960, 41: 233–238. (*Health Dept., City Hall, Cardiff, Wales)

An account is given of a tuberculin survey of the child population of Cardiff, Wales, which numbered ¼ million. One-fifth of the children less than school age and 83 per cent of the school population were tuberculin tested in 1 year. Three of 35 tuberculin-positive children younger than school age and 7 of 1,214 (6 per 1,000) unvaccinated school children with strongly positive tuberculin tests were found to have active tuberculosis. Thirteen of 1,011 (13 per 1,000) adult household contacts of tuberculin-positive infants and hypersensitive school children were found to have active tuberculosis. This survey shows that, using the Heaf test, it is possible to tuberculin test 83 per cent of the school population of a large urban area without employing a large number of medical personnel for the purpose. —M. J. Small

The Heaf Multiple Puncture Tuberculin Test. S. R. Andersen* and M. H. D. Smith. *AMA J Dis Child*, June, 1960, 99: 764–769. (*N.Y.U.-Bellevue Med. Center, N. Y.)

A series of 711 Bellevue Hospital Clinic and general ward patients between the ages of 1 month and 15 years were given Heaf tests on one forearm and intradermal 5-TU Mantoux tests on the other, and the patients were subsequently seen for reading of the tests. The Heaf test was positive in all 48 patients who reacted to the 5-TU Mantoux test. In addition, 22 patients were doubtful or positive reactors to the Heaf test, although they were negative to the 5-TU Mantoux test. Of these, 17 were tested with 100 TU and 250 TU, and 13 were positive. Thus the Heaf test appeared highly specific, although more sensitive than the 5-TU Mantoux. Omitting from consideration the Heaf test results which were only "questionable 1+," there were still 13 patients with positive Heaf and negative 5-TU Mantoux reactions. The intensity of the positive reactions to both tests was roughly parallel for the smaller reactions. In persons with marked sensitivity to tuberculin, the Heaf test produced fewer unpleasant reactions than did the Mantoux test. The simple equipment needed for the Heaf test, the relative ease of its administration, the stability of the glycerinated PPD (Protoderm) employed, and the absence of false negative tests render it the most satisfactory tuberculin test presently available for tuberculin testing large numbers of persons (after authors' summary).—M. J. Small

$a_2\,CO_3 + Na_2\,SO$

$Ag\,Br + Ag_2$

$g\,NO_3 + H\,NO_3$

$NH + SO_4$

$S + K\,Br$

$SO_3 + Ag$

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No specialty	50	11.46
Starred pulmonary specialist	84	19.27
Pulmonary specialist	24	5.50
Starred internist	85	19.49
Starred surgeon	31	7.10
Surgeon	3	.68
Starred thoracic surgeon	27	6.19
Starred radiologist	7	1.60
Starred public-health specialist	5	1.14
Starred pathologist	3	.68
Starred pediatrician	3	.68
Starred otologist	2	.45
Starred and unstarred specialists in allergy, bacteriology, gastroenterology, hospital administration, industrial medicine, OALR, OBG, orthopedic surgery, physical medicine—one each	9	2.06
No information	17	3.89
	350	80.19
Institutional subscribers	86	19.72
	436	99.91

MAJOR PROFESSIONAL INTEREST

	No.	%
General private practice	22	5.04
Primary interest in internal medicine and pulmonary diseases	170	38.99
GP with interest in pulmonary diseases	24	5.50
Physician in advanced training	17	3.89
Full-time hospital staff	76	17.43
Full-time medical-school staff	7	1.60
Hospital administration	2	.45
Special research	1	.22
General public-health practice	10	2.29
Retired	3	.68
Not in practice	1	.22
No information	17	3.89
	350	80.19
Institutional subscribers	86	19.72
	436	99.91

AGE OF PHYSICIAN

	No.	%
No information	17	3.89
No age given	1	.22
30–34	10	2.29
35–39	55	12.61
40–44	58	13.30
45–49	50	11.46
50–54	51	11.69
55–59	37	8.48
60–64	35	8.02
65 and over	36	8.25
	350	80.21
Institutional subscribers	86	19.72
	436	99.93

POPULATION

	No.	%
Under 10,000	56	12.84
10–25,000	39	8.94
25–50,000	44	10.10
50–100,000	38	8.71
100–200,000	32	7.33
200–500,000	48	11.00
500–1,000,000	39	8.94
Over 1,000,000	54	12.38
	350	80.24
Institutional subscribers	86	19.72
	436	99.96

BREAKDOWN OF INSTITUTIONAL SUBSCRIPTIONS

Federal Hospital		General Hospital		Special Hospital		Laboratory		Medical Schools		College University		Society Library		Population	
3		2		5		2		0		1		0		Under 10,000	
3		2		1		0		0		1		0		10–25,000	
0		2		4		0		3		2		1		25–50,000	
1		1		1		0		1		2		2		50–100,000	
2		0		1		1		0		0		2		100–200,000	
3		6		0		0		0		1		4		200–500,000	
4		3		2		0		0		1		0		500–1,000,000	
2		4		1		1		2		0		6		Over 1,000,000	
18	4.12%	20	4.58%	15	3.44%	4	.91%	6	1.37%	8	1.82%	15	3.44%	86	19.72%

Percentages figured only to second decimal point

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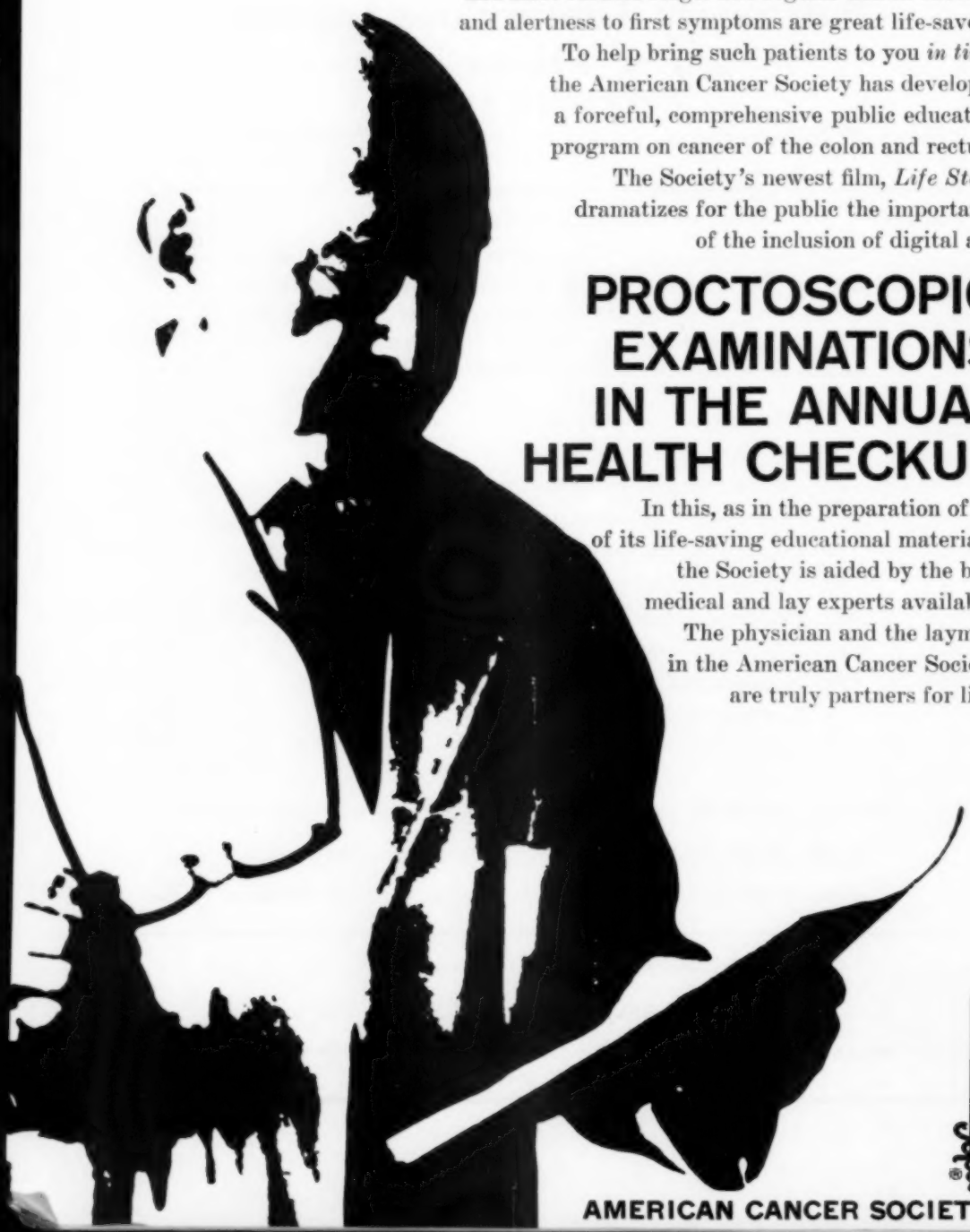

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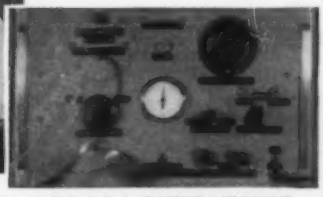

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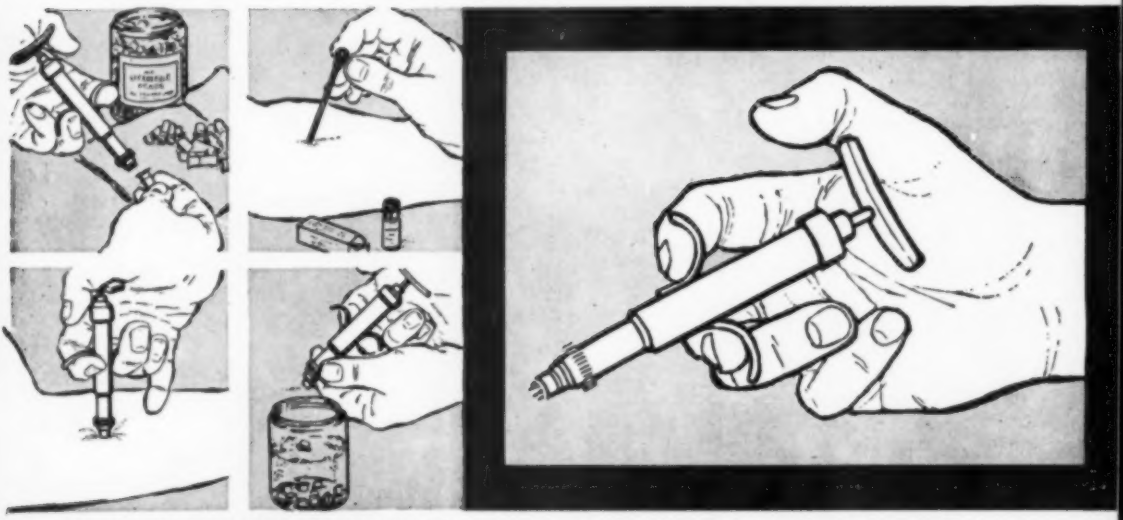

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Top, right... Place a drop of tuberculin PPD on cleansed forearm.

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